



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 64

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 64

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Volume 64



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Contents

CONTRIBUTORS	vii
PREFACE	ix

Amino Acids as Synthons for Heterocyclic Compounds

MIHA TIŠLER AND PATRIK KOLAR

I. Introduction	2
II. Three-Membered Rings	3
III. Four-Membered Rings	4
IV. Five-Membered Rings	6
V. Six-Membered Rings	28
VI. Seven-Membered Rings	35
VII. Bicyclic 5-5 Ring Systems	36
VIII. Bicyclic 5-6 and 5-7 Ring Systems	45
IX. Bicyclic 5-5 and 5-6 Ring Systems with Three Heteroatoms	47
X. Quinolines and Isoquinolines	48
XI. Benzopyrones	50
XII. Other Fused Bicyclic 6-6 and 6-7 Rings	51
XIII. Tricyclic and Polycyclic Ring Systems	55
References	63

Tropones, Tropolones, and Tropylium Salts with Fused Heterocyclic Rings Part 1: Synthesis

GUNTHER FISCHER

I. Introduction	82
II. Syntheses	86
References	145

Iminophosphoranes: Versatile Tools in Heterocyclic Synthesis

HEINRICH WAMHOFF, GABRIELE RICHARDT, AND STEPHAN STÖLBEN

I. Introduction	160
II. Synthesis of Iminophosphoranes	160
III. General Properties	168
IV. Biological Activity	173
V. Aza-Wittig Reaction	174
VI. The Aza-Wittig Reaction: A Versatile Principle in Heterocyclic Synthesis	182
VII. Iminophosphoranes as Versatile Starting Materials in the Three-Component Reaction: Iminophosphorane–Heterocumulene–Heteroarene	231
VIII. Conclusion and Outlook	239
References	240

Recent Developments in Ring–Chain Tautomerism

I. Intramolecular Reversible Addition Reactions to the C=O Group

RAIMONDS E. VALTERS, FERENC FÜLÖP, AND DEZSŐ KORBONITS

I. Introduction	252
II. Intramolecular Reversible Addition Reactions to the C=O Group	258
References	311

S-, *Se*-, and *Te*-(Perfluoroalkyl)dibenzothiophenium, -selenophenium, and -tellurophenium Salts

TERUO UMEMOTO

I. Introduction	323
II. Synthesis	324
III. Properties	328
IV. ¹⁹ F Nuclear Magnetic Resonance	329
V. Perfluoroalkylation	329
VI. Kinetics of Trifluoromethylation	337
References	338

1,3-Oxazinium and 3-Azapyrylium Salts

SERGEI M. LUKYANOV

I. Introduction	341
II. 5,6-Dihydro-4 <i>H</i> -1,3-Oxazinium Salts	342
III. 1,3-Oxazinium Salts	346
IV. 3-Azapyrylium Salts	350
V. 1,3-Oxazinium Salts Having Two Nitrogen Atoms	357
VI. Functionalized 1,3-Oxazinium Derivatives	360
VII. Spectral Properties of 1,3-Oxazinium Derivatives	361
References	363

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Preface

Volume 64 of our series consists of six chapters covering an exciting range of topics in contemporary heterocyclic chemistry. M. Tišler and P. Kolar (Ljubljana, Slovenia) review applications of various amino acids in the synthesis of chiral heterocycles which have become of great importance as synthons for the preparation of a variety of optically active derivatives.

The synthesis of tropones, tropolones, and tropylium salts with fused heterocyclic rings forms the first part of a projected two-chapter sequence by G. Fischer (Leipzig, Germany). It is planned that the structure, reactivity, and applications of these compounds will be discussed in a further contribution in a subsequent volume.

A comprehensive overview of the multifaceted use of iminophosphoranes as versatile reagents in heterocyclic synthesis is provided by H. Wamhoff, G. Richardt, and S. Stölben (Bonn, Germany).

R. E. Valters (Riga, Latvia), who provided a definitive monograph on ring-chain tautomerism ten years ago, is joined by F. Fülöp (Szeged, Hungary) and D. Korbonits (Budapest, Hungary) in the first of a two-part contribution to our series which will cover more recent developments. The present chapter is concerned with ring-chain tautomerism involving intramolecular reversible addition reactions to carbonyl groups.

(Perfluoroalkyl)dibenzothiophenium salts and their selenium and tellurium analogs are novel perfluoroalkylating agents. The synthesis and reactivity of these compounds are covered by T. Umemoto (Ibaraki, Japan). Finally, the first detailed survey of the chemistry of 1,3-oxazinium and 3-azapyrylium salts for over twenty years is provided by S. Lukyanov (Rostov-on-Don, Russia).

A. R. KATRITZKY

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Amino Acids as Synthons for Heterocyclic Compounds*

MIHA TIŠLER AND PATRIK KOLAR

Faculty of Chemistry and Chemical Technology, University of Ljubljana, 61000 Ljubljana, Slovenia

I. Introduction	2
II. Three-Membered Rings	3
III. Four-Membered Rings	4
IV. Five-Membered Rings	6
A. Pyrroles	6
1. Incorporation of Only the Amino Group of Amino Acids into the Pyrrole Ring	6
2. Cyclizations Involving Two Functional Groups	6
3. Cyclizations Involving Other Internal or External Functional Groups	7
4. Cyclizations of Imines of Amino Acids	8
5. Addition of Amino Acids to Unsaturated Compounds	9
6. From Unsaturated Amino Acids	11
7. From Aminomalonates	12
8. From β -Amino Acids by Miscellaneous Methods	13
B. Furans	14
C. Thiophenes	16
D. Pyrazoles	17
E. Imidazoles	18
F. Isoxazoles	19
G. Oxazoles	21
H. Isothiazoles	23
I. Thiazoles	24
J. Five-Membered Rings with More Than Two Heteroatoms	25
V. Six-Membered Rings	28
A. Pyridines	28
B. Pyrimidines	31
C. Pyrazines	32
D. Pyrones	33
E. Oxazines	33
F. Thiazines	34
G. Six-Membered Rings with Three Heteroatoms	34
VI. Seven-Membered Rings	35
VII. Bicyclic 5-5 Ring Systems	36
A. One Heteroatom Adjacent to the Ring Junction	36

* Dedicated to Professor Dr. Richard Neidlein on the occasion of his 65th birthday.

B. One Heteroatom Not Adjacent to the Ring Junction	38
C. Systems with One Heteroatom at a Ring Junction	39
D. Systems with Two Heteroatoms	41
1. One Heteroatom in Each Ring	41
2. One Heteroatom at a Ring Junction	43
VIII. Bicyclic 5-6 and 5-7 Ring Systems	45
IX. Bicyclic 5-5 and 5-6 Ring Systems with Three Heteroatoms	47
X. Quinolines and Isoquinolines	48
XI. Benzopyrones	50
XII. Other Fused Bicyclic 6-6 and 6-7 Rings	51
XIII. Tricyclic and Polycyclic Ring Systems	55
A. Pyrroloindoles	55
B. Tetrahydro- β -carbolines	55
C. Other Systems	57
References	63

For proteinogenic amino acids common three-letter abbreviations are used: Ala—alanine, Gly—glycine, Gly-OMe—glycine methyl ester, and so forth.

I. Introduction

Although amino acids (AAs) are usually regarded as important building blocks for peptides and proteins, in the last decade they have become important synthons in the construction of various heterocyclic systems. For various purposes of asymmetric synthesis, 375 chiral carbon fragments are available, among which are AAs as inexpensive stereochemically pure synthons (84MI1). There are many examples of biosynthesis in Nature that use AAs as starting compounds, i.e., alkaloids, pyrimidines, and purines. Last, but not least, the biochemical path involves the incorporation of L-Cys in penicillins and biotin.

α -Amino acids can act as multifunctional synthons. Quite often a combination of the amino and other functional groups occurs in the formation of a heterocycle (87MI1).

For the asymmetric synthesis of AAs, several heterocyclic systems have been used as chiral auxiliaries. Because these transformations are not included in this review article, we cite here some of the most important articles or reviews concerning this topic. For asymmetric derivatization of Gly, bis-lactim ethers of 2,5-piperazinediones (83PAC1799; 85CS105), or oxazinones (88JA1547) were used. Seebach introduced a method based on the principle of self-reproduction of stereogenic centers involving various heterocyclic systems (1,3-dioxolanes, 1,3-oxazolinones, imidazolidinones, and related systems) (86MI1). A general review is given also in a book (89MI1).

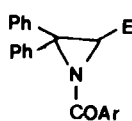
This review does not include many of the well known transformations of AAs that have already been reviewed. These include hydantoins (imidazoline-2,4-diones) or thiohydantoins, obtained from AAs and isocyanates or isothiocyanates [77H1227; 85AHC(38)177], as well as the synthesis and use of chiral thiazolidine-2-thiones (from Cys) [89AHC(45)1], piperazine-2,5-diones resulting from dimerization of AAs and related lactim ethers (93AHC187), azlactones (oxazolin-5-ones) (46OR198; 78AG493), sydnones (64CRV129), oxazoles via the Dakin–West reaction (88CSR91), oxazolidine-2,5-diones (NCA, *N*-carboxy- α -amino acid anhydrides—from α -AAs and phosgene) important in peptide synthesis (87MI2), β -lactam antibiotics, and cyclic peptides and macrocycles containing AAs. The chemistry of pyroglutamic acid has also been reviewed (91MI1).

In this review reactions are described which start from AAs, some β -AAs, and unsaturated AAs. Aromatic AAs having the amino and carboxylic group attached directly to the aromatic or heteroaromatic ring are not included.

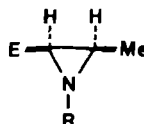
II. Three-Membered Rings

There are only few reports concerning AA as a starting material for the preparation of heterocyclic three-membered rings. Most of them describe the preparation of aziridines. For example, the diphenylimine derivative of Gly-OEt, when treated with sodium hydride and arylacetyl chlorides, is transformed into aziridines **1** (89TL4717). There are several reports concerning *N*- and *O*-protected Ser and Thr, which are cyclized in the presence of a base to give substituted aziridines (68BCJ1353; 93JOC7848). However, a report on a similar transformation yielding aziridines (72BCJ1162) has been corrected since careful analysis showed that the reaction products are oxazolines (77BCJ917). The tendency of Thr derivatives to form aziridines is much stronger than in the case of Ser and less dependent on several factors. This was also demonstrated when a *p*-toluidide derivative of *N*-Cbz-L-Thr was treated with triphenylphosphine and diethyl azodicarboxylate (DEAD) to give an aziridine, whereas a similar L-Ser derivative was transformed into an azetidine derivative (81JOC1229). After being reductively alkylated with benzaldehyde, D-Thr ester is easily transformed into **2** with TPP in good yield (85JOC4515).

Diazotization of AAs proceeds via the corresponding α -hydroxy acids to oxiranes. From chiral starting material chiral oxiranes are obtained with retention of configuration. This synthetic principle is generally applicable (79T1601; 89TL5505).



(1)



(2)

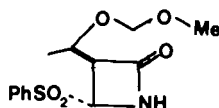
In a similar manner, nitrosation of L-Cys alkyl esters resulted in the formation of optically pure (*S*)-thiirane carboxylates **3**. From the L-isomer the corresponding (*R*)-thiirane carboxylates were obtained. The reaction is interpreted as an S_N2 displacement of the diazonium group by the sulfur atom [76CC234; 79JCS(P1)1852].



(3)

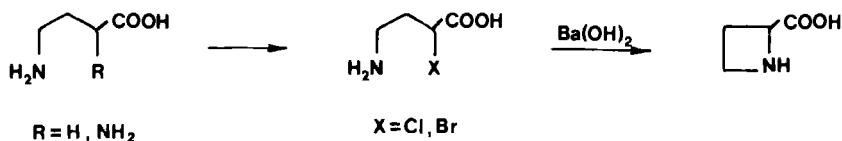
III. Four-Membered Rings

Derivatives of azetidine were prepared from α -, β -, or γ -AA. L-Threonine was transformed in eight steps into **4**

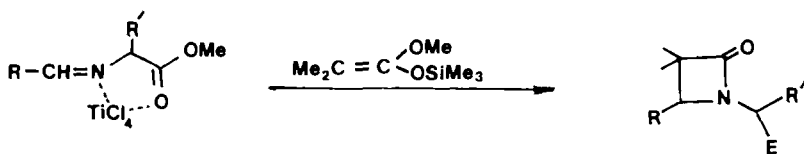


(4)

a key intermediate of the carbapenem and penem antibiotics (83TL1037). A related derivative was also prepared from a similar γ -hydroxy- α -AA (85JOC3457). Several examples of cyclodehydration of β -AAs are described. For these purposes cyclization was performed with mesyl chloride (91TL2299), with triphenylphosphine (TPP) and pyridyl disulfide (Mukaiyama reagent) (81JA2406), with diphenylphosphinic chloride (88CC1242),



SCHEME 1



SCHEME 2

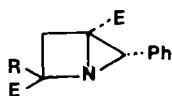
or with bis(5'-nitro-2'-pyridyl)-2,2,2-trichloroethylphosphate (NPTP) (87TL2735). (2*R*,3*R*)-*t*-Butyl 3-(*N*-benzoylamino)-2-methylbutanoate was converted into an azetidinone derivative after treatment with a solution of $\text{BF}_3 \cdot \text{THF}$, trifluoroacetic acid (TFA), and 2-chloro-1-methylpyridinium iodide (94JOC649). Azetidine 2-carboxylic acid, a natural nonproteinogenic AA, was synthesized either from Glu or from 4-aminobutanoic acid via the corresponding halogenated acids (Scheme 1) [55N(L)(176)347; 56BJ323].

α -Amino acids were transformed into the corresponding imines; and after the complexes with TiCl_4 were formed, these underwent cycloaddition with dimethylketene methyl trimethylsilyl acetal to give the corresponding β -lactams (Scheme 2) (80TL2081).

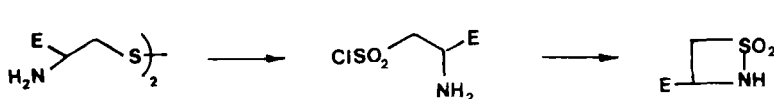
N-Protected derivatives of Ser or Thr were cyclized into the corresponding β -lactones in low or moderate yields. For these purposes, either dicyclohexylcarbodiimide (DCC) (70CB788) or its isopropyl analog (59JA6086) *p*-bromobenzenesulfonyl chloride in pyridine (89JOC2311) or Mitsunobu conditions (TPP and DEAD) were used [85JA7105; 88JA2237; 90H(31)79]. A substituted β -lactone was also prepared from esterified and *N*-protected L-Asp in three steps (89T6319).

There are two reports describing the preparation of derivatives of 1,2-thiazetidine-1,1-dioxide. The sulfur atom in L-cystine diethyl ester was oxidized and the corresponding sulfonyl chloride was cyclized with ammonia (Scheme 3) (60CB784). A similar transformation used protected β -homocysteine as starting material (94LA251).

A derivative of a fused three- and four-membered ring **5** (aza-1-bicyclo-[2.1.0]pentane) was obtained from Ala after alkylation with methyl α -bromoacrylate (85T2707).



(5)



SCHEME 3

IV. Five-Membered Rings

A. PYRROLES

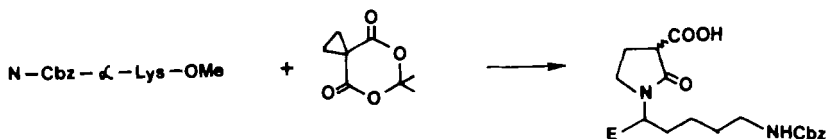
1. Incorporation of Only the Amino Group of Amino Acids into the Pyrrole Ring

Cyclic acetals such as 2,5-diethoxytetrahydrofuran react with the amino group of an AA ester to give the corresponding pyrrole derivative. The same transformation could also be performed by free AA or dipeptides (68CCC1307; 88OPP414; 91JA3513).

In a similar manner, *N*-Cbz- α -Lys-OMe reacted with an electrophilic cyclopropane derivative, and a mixture of diastereomeric γ -lactams was isolated. The reaction is postulated to proceed by an attack of the amino group on the methylene group with subsequent cyclization (Scheme 4) (85JOC3631).

2. Cyclizations Involving Two Functional Groups

It was found that AAs having an additional remote amino or carboxylic group are easily transformed into the corresponding cyclic pyrrole derivatives or into other six- or seven-membered cyclic systems, depending on the position of the additional functional group. From Cbz-L-Asp-O-*t*Bu in alkaline solution a 3-aminopyrrole-2,5-dione was obtained (63JOC1251). Even in a polypeptide chain with an asparagine unit at the *N*-terminal position, the same reaction takes place (77CB1). There are many examples of cyclizations of Glu or its derivatives into pyrroles. When heated at 180–200°C, L-Glu is transformed into (*R*)-5-oxopyrrolidine-2-carboxylic acid (pyroglutamic acid) [09ZPC(64)447; 42JA1021; 78S752], but the same reaction occurs when heating the aqueous (78S290; 79CB3703) or toluene solution (80TL2443) without racemization. Cyclizations were reported via the mixed-anhydride method with acetic acid (40JCS706), with thionyl chloride (54CCC365), or by heating with aniline at about 200°C (78S684). Cyclization of Glu was also achieved with alcoholic alkoxide solution (43JCS39; 51JCS104). In the synthesis of tylophorine, an intermediate with a pyrrole

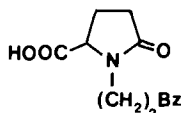


SCHEME 4

ring was obtained from *N*-substituted Glu in methanolic acetic acid (83JOC4222). Another way of cyclization is to displace the amino group by a chlorine atom; ring closure occurs in the presence of a base (52JBC587; 53BCJ53). The reaction was applied in the case of ornithine. Moreover, an alkyl side chain in Ile was chlorinated photochemically and cyclization occurred in an alkaline solution. In this manner the *trans* isomer of 3-methylproline was prepared from L-Ile (66JA3624) and the *cis* isomer was obtained from D-*allo*-Ile.

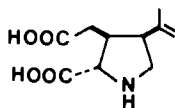
3. Cyclizations Involving Other Internal or External Functional Groups

The main synthetic transformation involves *N*-alkylation or *N*-acetylation of an AA with subsequent cyclization, but a reactive methylene group in glycine can also be involved in the reaction (90S389). L-Glu was alkylated by β -diethylaminopropiophenone in 10 *N* hydrochloric acid to give **6** in moderate yield (63JOC2779). Fully protected D-Ser was alkylated at the amino group to give a 3-methyl-2-butenylamino group, and thereafter in a series of transformations α -kainic acid **7** was prepared (90T7263). Cyclizations to pyrroles were also reported from *N*-cyanoethyl α -AA (65JOC194) and ethyl *N*-ethoxycarbonyl-*N*-(2-ethoxycarbonylethyl)glycinate (64JA5293) or from a dipeptide with D-Glu at the *N*-terminal position (88TL5057). *N*-[β -(Ethoxycarbonyl)ethyl]-*N*-(4-methoxyphenyl)glycinate was transformed by an intramolecular Dieckmann reaction into 1-aryl-3-ethoxycarbonylpyrrolidin-4-one, an intermediate in the synthesis of the pyrrolo[3,4-*c*]pyrido[2,3-*d*]pyrimidine ring system (89JOC220).



(6)

There are two examples in which the carboxylic group is first reduced to an alcohol. In this manner a multistep transformation yielded kainic acid **7** with the correct configuration at all three chiral centers (82JA4978). A similar reaction afforded (–)- or (+)-*trans*-2,5-dimethylpyrrolidine from L- or D-Ala (87TL2083).



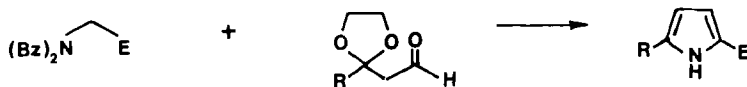
(7)

N-Acyated AAs were also used as starting materials. *N*-Acylation was performed with ethoxycarbonylacetyl chloride and sodium alkoxides were used for cyclization [72JCS(P1)2121; 76BCJ3287; 78TL3173; 89SC2573].

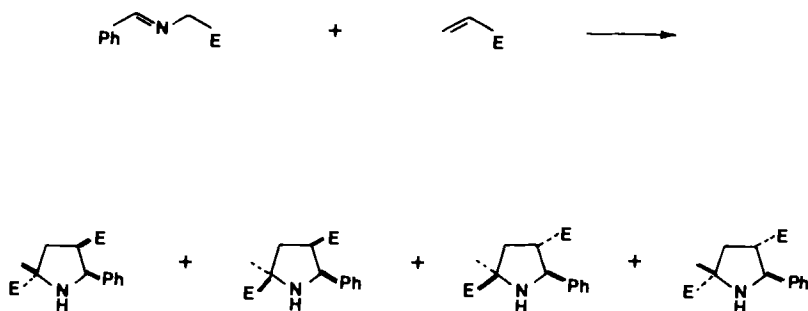
Enamines, which are formed in the reaction between AA esters and 1,3-dicarbonyl compounds are transformed into pyrroles under basic conditions or with trifluoroacetic anhydride (TFAA) [75S726; 82S157; 90H(31)1049, 90S389; 93JHC1253]. Alkylation can also occur at the glycine methylene group and a number of 5-substituted pyrrole-2-carboxylates were prepared from *N,N*-dibenzylglycinate and β -ketoacetals (Scheme 5) (89SC763) or Gly and 1,3-diketones (82S157).

4. Cyclizations of Imines of Amino Acids

Imines (Schiff bases) obtained from AA and aromatic aldehydes or ketones either react with alkenes and alkynes or thermally to yield pyrrolidines. The reaction has been elaborated in detail, particularly with respect to stereochemistry. Treatment of *N*-benzylidene Gly-OMe with NaH in tetrahydrofuran (THF) resulted in the formation of the metallated azomethine ylide, which underwent a 1,3-dipolar cycloaddition with methyl acrylate to give a mixture of all four possible pyrrolidones; a Michael adduct was also formed as a side product (Scheme 6). The selectivity of the cycloaddition is improved in the presence of triethylamine, *t*-BuOH, and MeOH and different combinations of metal salts; MeCN, dimethyl sulfoxide (DMSO), and *N,N*-dimethylformamide (DMF) or benzyltrimethylammonium methoxide (BTAM) also affect the regio- and stereospecificity of these cycloadditions (89BCJ2196, 89TL4727). Cycloadditions show substantial rate enhancement in the presence of Brønsted and Lewis acids (87T5887). Chelation between lithium ion and the imine nitrogen and between lithium ion and the carbonyl oxygen is in part responsible for the high stereoselectivity (88JOC1384). Cycloaddition competes with Michael addition, and the ratio of products depends on the reaction conditions and the metal ion (90JOC4411). Acrylonitrile, diethyl maleate or fumarate, β -nitrostyrene, *N*-methyl- or *N*-phenylmaleimide, maleic anhydride, benzylidene malonate or benzylidene malonodinitrile, and 1,4-naphthoquinone were used as dipolarophiles (78CC109, 78TL2885; 79TL3877; 80TL2461; 88JOC1384, 88T5361; 92T3557). Sometimes, single isomers are obtained (78CC109). For cycloadditions α,β -unsaturated ketones (91TL3727),



SCHEME 5



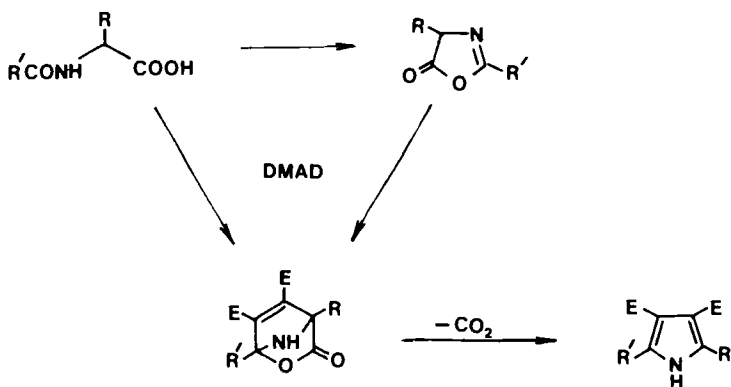
SCHEME 6

methyl propiolate, ethyl phenylpropiolate, or dimethyl acetylenedicarboxylate (DMAD) also were used (78CC109; 90T6467).

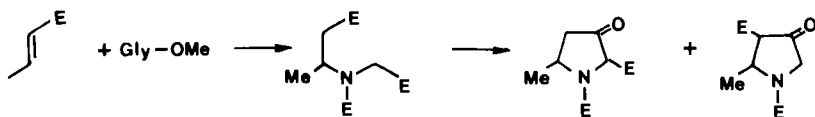
N-Acyl AAs could be transformed *in situ* into the azlactones; or if these compounds are used as a starting material, they react with DMAD to give a bicyclic cycloadduct which eliminates carbon dioxide to give the corresponding pyrrole derivative (Scheme 7) (70CB2356, 70CB2611).

5. Addition of Amino Acids to Unsaturated Compounds

The adduct between Gly-OMe and methyl crotonate underwent a Dieckmann cyclization after *N*-carboxylation to give a mixture of isomers that could be separated (Scheme 8) (75BBR502; 77JOC1000). The reaction was used to prepare 3-hydroxy-5-methylproline; 4-hydroxy-5-methylproline also was synthesized in a similar manner (65N391).



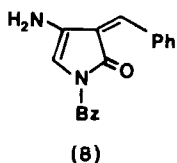
SCHEME 7



SCHEME 8

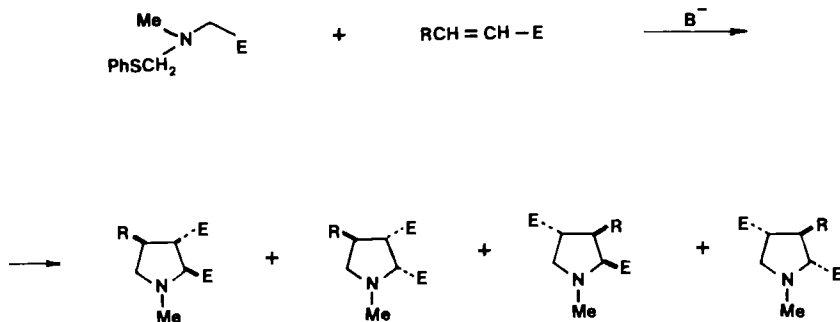
Esters of *N*-(phenylthiomethyl)AAs undergo a base (NaH)-promoted addition to unsaturated esters to give a mixture of diastereoisomeric regioisomers (Scheme 9) (84TL1579).

Gly-OEt was also added to ethyl 3-perfluoroalkylpropynoates which were transformed in several steps into 5-perfluoroalkyl-substituted 1-methyl-2-ethoxycarbonylpyrrolidin-3-ones (90T6705). 3-Propyl- and 4-propylprolines and 4-*n*-pentylproline were synthesized from diethyl acetamidomalonate and an unsaturated aldehyde (67JA2459; 72JMC1255). Ethyl benzyldienecyanoacetate reacts with hippuric acid to give the pyrrole **8** (87H2323).

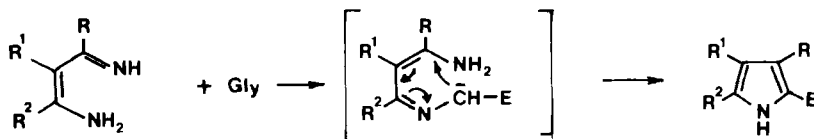


Derivatives of azabutadiene react with Gly-OEt to give pyrrole-2-carboxylates. This reaction, which is assumed to occur via an azapentadienyl anion, allows the synthesis of 3,5-diarylpyrrole-2-carboxylates in a regioselective manner (Scheme 10) (82JOC1696).

Esters of AAs react under basic conditions with 2-substituted vinamidinium salts to give 4-substituted 2-carbethoxypyrroles. In a similar manner a variety of 3-aryl-3-chloropropeniminium salts react with esters of either



SCHEME 9



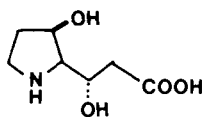
SCHEME 10

Gly or sarcosine to give the corresponding pyrroles in a regioselective manner (Scheme 11) (90JOC4735; 92JOC5480).

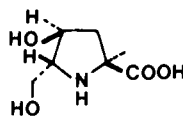
The azomethine ylide formed *in situ* from benzaldehyde and an *N*-alkyl AA reacts with an alkene to give a mixture of diastereomeric pyrrolidines (85TL2775).

6. From Unsaturated Amino Acids

In a multistep reaction sequence, *N*-Boc-L-allylglycine was converted into detoxinine **9** (84TL4133). Hydroxymethyl L-allylglycine was converted via a lactone into (–)-bulgenicine **10** (86TL6079).

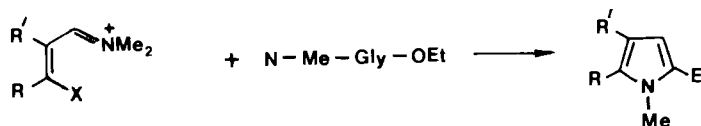


(9)



(10)

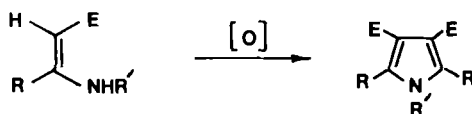
Pyrroles can also be obtained from aminocrotonates by oxidation. The transformation is actually a dimerization resulting from a two-electron oxidation of the enamine (Scheme 12) (83T793). 1,4-Addition of nitromethane to the vinilogenous ester of AA in presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave a 1:1 diastereomeric mixture of adducts which, upon reduction, spontaneously cyclized into a mixture of pyrrolidinones, formed in a ratio of 8:2 (Scheme 13) (93TL7529).



a: $R = H$, $R' = Ar$, $X = NMe_2$

b: $R = Ar$, $R' = H$, $X = Cl$

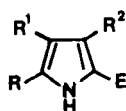
SCHEME 11



SCHEME 12

7. From Aminomalonates

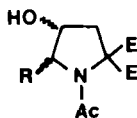
Diethyl aminomalonate reacts with 1,3-diketones in boiling acetic acid to the corresponding pyrrolecarboxylates **11** (87JOC3986). From *N*-acetamidomalonate and acroleins, pyrrolidines were prepared and they were further transformed into functionalized pyrroles, which are a part of the antibiotic lincosmycin and an antimalarial agent (67JA2459; 72JMC1255).



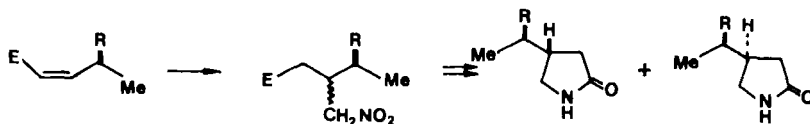
(11)

A substituted acetamidomalononic ester, tetraethyl 1-acetamido-4-hydroxybutane-1,1,3,3-tetracarboxylate, was used in the preparation of *cis*- and *trans*-pyrrolidine-2,4-dicarboxylic acids, cyclic analogs of glutamic acid (91TL3049).

A new synthetic method for 4-hydroxyproline was devised from *N*-acylated diethyl aminomalonate. In the first step this reacts with acrolein in the presence of a base to give **12** (90JHC507).



(12)

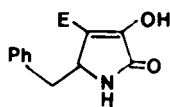


R = NHBoc

SCHEME 13

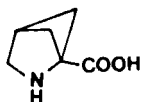
8. From β -Amino Acids by Miscellaneous Methods

In connection with the synthesis of cytohalasin B, a pyrrole derivative **13** was prepared from methyl (*S*)-3-aminophenylbutyrate (78JA7775). In connection with the synthesis of 1,2,4-triazolo[4,3-*a*]pyrazine derivatives with human Renin inhibitor activity, a β,γ -diamino acid derivative was transformed into a pyrrolidin-2-one (91JMC151).



(13)

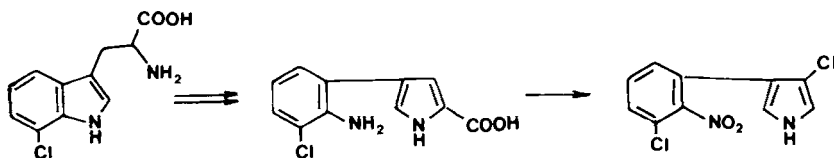
From Ser via methyl 2-benzamido-3-chloropropionate, an azahexadiene was prepared which was photocyclized and hydrolyzed to the bicyclic amino acid **14** which is found in the *Atelia Herbert Smithii* plant (88JOC4793).



(14)

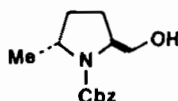
The pyrrole ring was also annelated to C₆₀-fullerene with sarcosine and paraformaldehyde to give the fulleropyrrolidine (93JA9798).

The ring opening of the pyrrole part of Trp with subsequent incorporation in a new pyrrole ring represents a special example. This sequence was observed when the antibiotic pyrrolnitrin was isolated from cultures of Gram-negative bacteria *Pseudomonas aureofaciens* to which D-Trp and sodium chloride were added. The compound was formed from 7-chlorotryptophan (Scheme 14) (80AG855). A similar transformation was observed in the case of 2-oxytryptophan which was treated with aqueous sodium hydroxide (85TL5871).

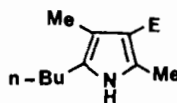


SCHEME 14

Chiral *trans*-2,5-dialkylpyrrolidines, which were used for the synthesis of ant-venom pyrrolizidines, were prepared in the following manner. D-Alanine was transformed into an pentenylamine which, upon intramolecular amidomercuration, yielded **15** (90TA561; 92JOC4401). From a protected AA amide, after a Grignard reaction and treatment of the aminoketone with ethyl acetoacetate, the tetrasubstituted pyrrole **16** was obtained [93H(35)843].



(15)



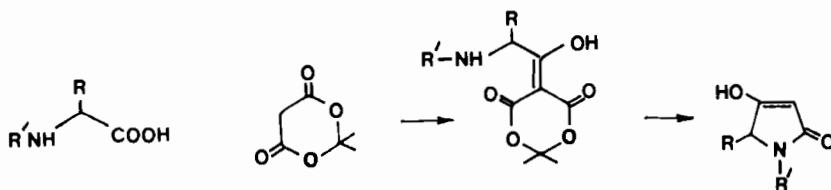
(16)

N-Protected AAs were activated *in situ* with isopropenyl chloroformate to give an intermediate anhydride which reacted with Meldrum's acid in the presence of 4-dimethylaminopyridine (DMAP) to give the corresponding 1,3-dioxane-4,6-dione. The reaction conditions are very stringent. Further transformation upon heating in an organic solvent yielded the pyrrole derivative (Scheme 15) [87JCS(P1)1177].

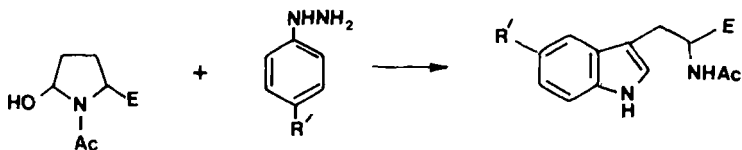
5-Hydroxyprolines react as aldehyde equivalents with arylhydrazines in the Fischer indole synthesis to give *N*-protected L-tryptophans in moderate to good yields (Scheme 16). The reaction is more suitable for the L series because of the price of the D-Pro starting material (84CPB2126).

B. FURANS

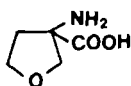
3-Amino-3-tetrahydrofurancarboxylic acid **17**, an oxygen cycloleucine analog, has been synthesized from D,L-homoserine by an intramolecular Mukaiyama aldol condensation in six steps (89TL1181). From D-Thr, L-muscarine **18** was synthesized in eight steps. The synthesis is highly stereoselective (85T5321).



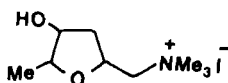
SCHEME 15



SCHEME 16



(17)

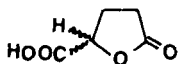


(18)

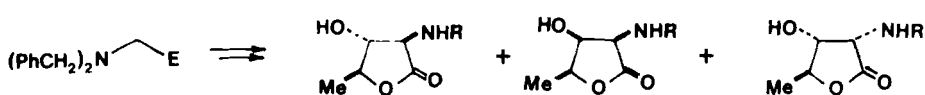
There are many reports describing the preparation of various butyrolactones from AAs. When *t*-butyl 2-dibenzylaminoacetate in the form of its Li-enolate was treated with (*S*)-*O*-benzylsuccinaldehyde, a mixture of four diastereoisomeric hydroxy-AAs was obtained. After separation and further treatment, three lactones were obtained (Scheme 17) (87T2317). Similar compounds were obtained from α -acylamino- γ -keto acids after cyclization (75CC905).

Butyrolactones were also prepared from esters of *N*-protected AAs after being treated with lithium diisopropylamide (LDA) at -78°C and thereafter with ethylene oxide (93JOC6966), or by chlorination of an AA having at least two carbon atoms in a side chain and subsequent hydrolysis (73LA560). In the latter case products are formed as a mixture of diastereoisomers in moderate yield.

Specific AAs were employed for particular substituted butyrolactones such as Asp (83TL2733; 87TL3167) or Glu (77TL423). When treated with nitrous acid, Glu is transformed in a stereospecific manner into the lactone acid **19**: L-Glu gives the (*S*)-lactone (68CCC2927; 71TL263), which served for the preparation of D-ribose (71TL263; 74T3547), for optically active epoxyterpenes (76TL2557) or hexadecanolactone (84T1061). In a similar



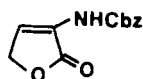
(19)



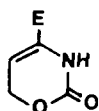
SCHEME 17

manner, L-Glu was converted into the (*R*)-lactone (74BCJ1704; 78T1449; 80MI1).

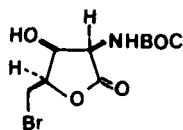
D,L-Homoserine was converted into the 3-*N*-Cbz-amino lactone (60JBC1103), which was also obtained from Met (78TL2243; 88CC1579). Vinylglycine, after being epoxidized with *m*-chloroperoxybenzoic acid (MCPBA), gave a mixture of isomeric epoxides which were treated with azide ion to afford a mixture of **20** and **21** in various proportions, depending on the reaction conditions (85JOC4515). Another unsaturated acid, (2*S*,3*R*)-2-amino-3-hydroxy-4-pentenoic acid, reacted with *N*-bromosuccinimide (NBS) to give the halolactone **22** as an intermediate in the synthesis of optically active 3,4-dihydroxyproline (85TL5307).



(20)

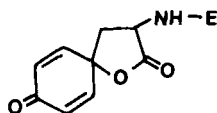


(21)



(22)

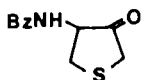
A spirolactone **23** was prepared by electrooxidation of *N*-carbomethoxytyrosine (63JA3702).



(23)

C. THIOPHENES

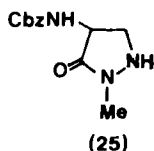
In a total synthesis of biotin from L-Cys, the thiophene derivative **24** is formed from *N*-protected carbomethoxymethylcysteine ester with sodium methoxide (44JA1756).



(24)

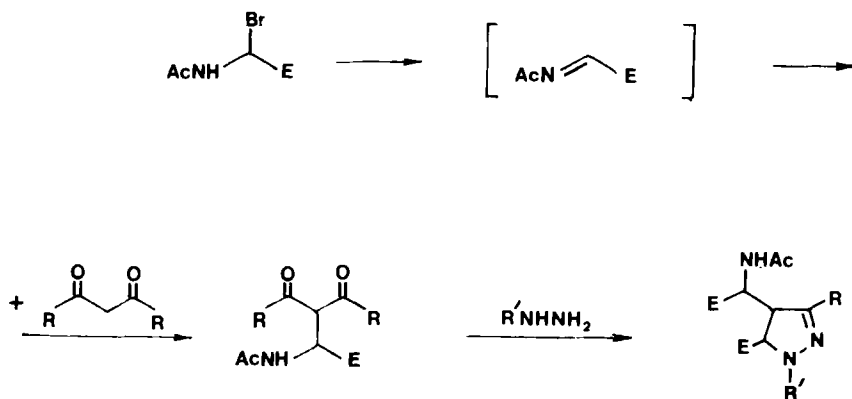
D. PYRAZOLES

The hydroxymethyl and carboxyl group of Ser can participate in pyrazole-ring formation, as shown in the transformation of *N*-protected L-Ser with the Mitsunobu reagent into a β -lactone which afforded the *N*-protected serine hydrazide upon treatment with methyl hydrazine. Cyclization to **25** was achieved by diisopropyl azodicarboxylate (DIAD) and TPP [90H(31)79].

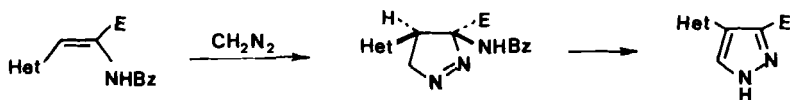


Another interesting synthesis started from *N*-acylglycine esters which generated *N*-acylimino esters *in situ* following bromination and base treatment. When these *N*-acylamino esters were alkylated with 1,3-dicarbonyl compounds and hydrazines, the corresponding pyrazoles were formed (Scheme 18) (88T5403).

The carbon-carbon double bond of an unsaturated AA reacts with 1,3-dipoles to give derivatives of pyrazole or isoxazole. When methanol is used as a solvent, the 1-pyrazolines primarily formed are tautomerized into 2-pyrazolines, which may eliminate benzamide or acetamide to give aromatic pyrazoles (Scheme 19) (88JHC851). Aromatization may also be affected with $\text{BF}_3 \cdot \text{Et}_2\text{O}$. The cycloadditions are stereospecific (85JOC3167). In a



SCHEME 18



SCHEME 19

similar manner, benzonitrilium *N*-phenylimide reacted as a dipolarophile to give the corresponding pyrazolines [92JCR(S)360].

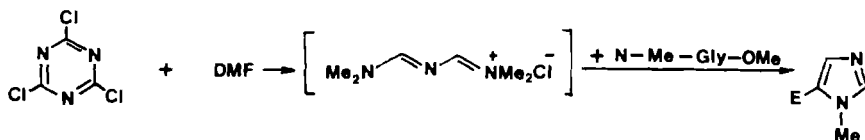
Addition of diazomethane to a dehydroalanine derivative gave a reduced pyrazole which afforded pyrazole-3-carboxylic acid in the presence of HCl (83TL2193).

E. IMIDAZOLES

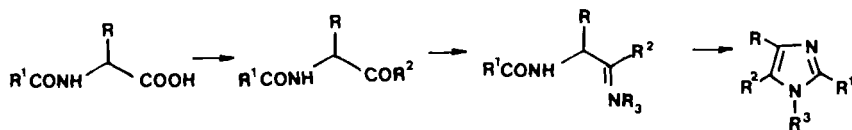
When acetylated and subjected to Hoffmann rearrangement, asparagine and its *N*-carbobenzoxy derivative are transformed into imidazolidin-2-one-4-carboxylic or 5-carboxylic acid [23HCA411; 37LA(529)1]. Methyl *N*-methylglycinate reacted with cyanuric chloride in the presence of DMF to give methyl 1-methylimidazole-5-carboxylate. The reaction proceeds via Gold's salt, which is formed from cyanuric chloride (Scheme 20) (94S247). When formylated esters of Gly or *N*-substituted derivatives were converted into the sodium enolate salts and treated with thiocyanate to give esters of imidazole-2-thione-5-carboxylic acid. These transformations are effective only with formylated or acetylated derivatives, and this synthetic approach also allows the preparation of imidazole (49JA644; 88S767). Amides of AAs react with 1,4-, 1,5-, or 1,6-keto esters. The keto group is utilized in imidazole-ring formation, and the side chain with the alkoxycarbonyl group can undergo cyclization to give condensed imidazoles (93JMC4214).

N-Acyl AAs, when transformed into α -acylaminoketones by the Dakin-West reaction, react with arylhydrazines, arylsulfonylhydrazines, or some primary amines to give the corresponding ketimines which undergo cyclodehydration with $\text{POCl}_3/\text{PCl}_5$ or TPP (Scheme 21) (78LA1916).

If the amino group of an AA is transformed into an amidine, cyclization can occur either with acetic anhydride in pyridine or with hydrazine to give



SCHEME 20

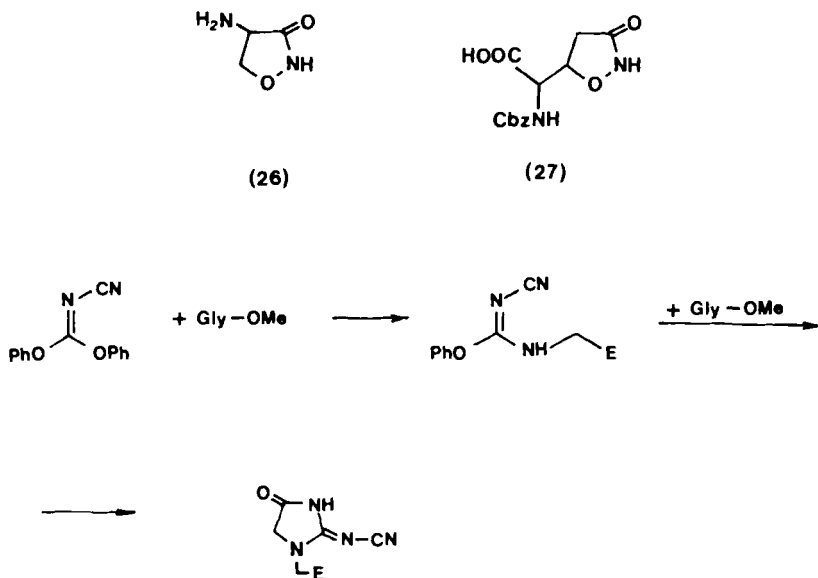


SCHEME 21

imidazol-5-ones [74SC289; 90H(30)393]. The transformation delineated in Scheme 22 represents a special case. This reaction has been applied to Gly-OMe and dimethyl aspartate to give imidazole derivatives. From methyl β -alaninate, however, a reduced pyrimidine was obtained (90T7803).

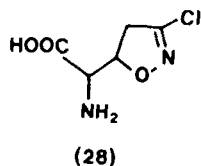
F. ISOXAZOLES

D,L-Cycloserine **26** and its 3-methyl analog, derivatives of isoxazolinone, were prepared from D,L-Ser or D,L-Thr. The transformation involved replacement of the hydroxyl group by chlorine and subsequent treatment with hydroxylamine (57HCA1531). After being transformed into its 3-chloro derivative, L-Glu was transformed in a multistep conversion into **27**, an intermediate in the synthesis of an antitumor isoxazole-5-acetic acid (81JA7357).

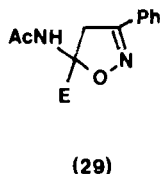


SCHEME 22

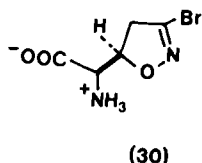
There are several examples of isoxazole-ring formation from unsaturated AAs. From a protected dehydroglutamic acid a 1 : 1 mixture of *erythro*- and *threo*-isoxazole derivative was obtained in several steps. Further elaboration afforded the antimetabolite **28**, which was previously isolated from *Streptomyces sviveus* (81JA942).



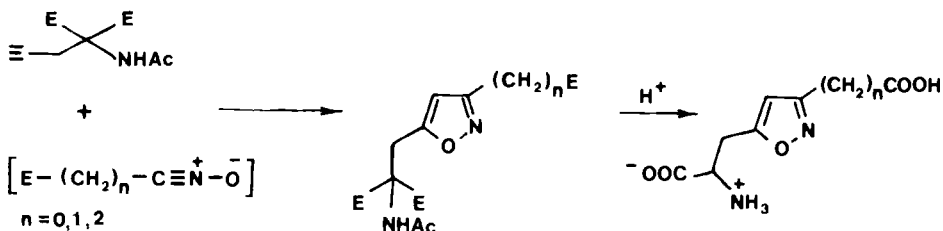
Addition to the multiple bonds in ethyl *N*-acetyl- α,β -dehydroalaninate by nitrones—for example, by phenylnitrone—afforded compound **29** (83TL2193).



Vinylglycine was used in the reaction with dibromoformaldoxime for preparation of a biologically active bromoisoxazoline **30**, prepared previously from tricholomic acid (79JA1054; 80TL229).



The product is a mixture of stereoisomers. The chloro analog, antimetabolite acivicin, was prepared in a similar manner from vinylglycine and dichloroformaldoxime (80JOC4817; 82TL4563). β -Isoxazolyalanines were prepared by 1,3-dipolar cycloadditions of nitrile oxides to substituted acetamidomalonates (Scheme 23) (92JMC107).

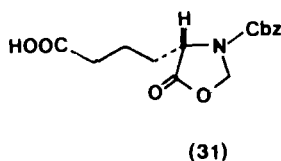


SCHEME 23

G. OXAZOLES

L-Serine methyl ester can be transformed into methyl oxazolidin-2-one-3-carboxylate with phosgene and aqueous potassium carbonate (90TL7407). Some AAs (Gly, Val, Phe) were transformed into their *N*-(2-chloroethylcarbamoyl) derivatives, and these can cyclize into oxazolines (Scheme 24) (83T2255). In boiling water they are transformed into hydantoin derivatives.

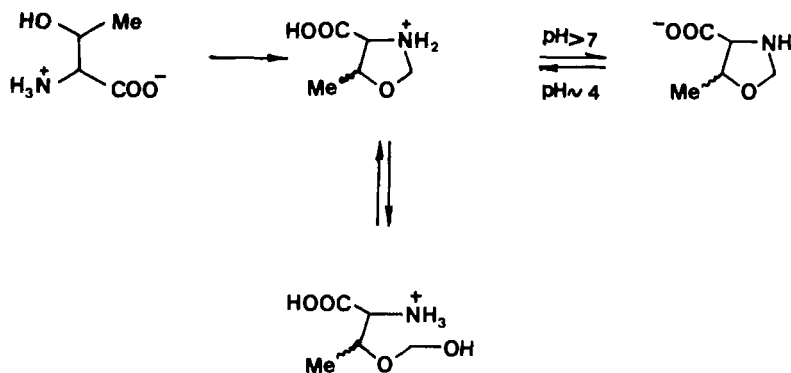
Aldehydes and ketones were used in many syntheses starting from an AA. The first total synthesis of porothramycin B, a potent natural antibiotic, used L-Glu as starting material. In the first step compound **31** was obtained from an *N*-protected AA and paraformaldehyde (84TL927; 88TL2231; 93TL2577).



A similar product is obtained from Asp (69CPB1679). *N*-Benzoyl or *N*-tosyl AAs also react in the same manner with formaldehyde or paraformaldehyde (57CB2906, 57JA5736; 59CB309). D,L-Threonine reacts with formaldehyde to give a protonated oxazolifidinecarboxylic acid, which is unstable and in equilibrium with the open chain methylol. After deprotonation, a stable



SCHEME 24

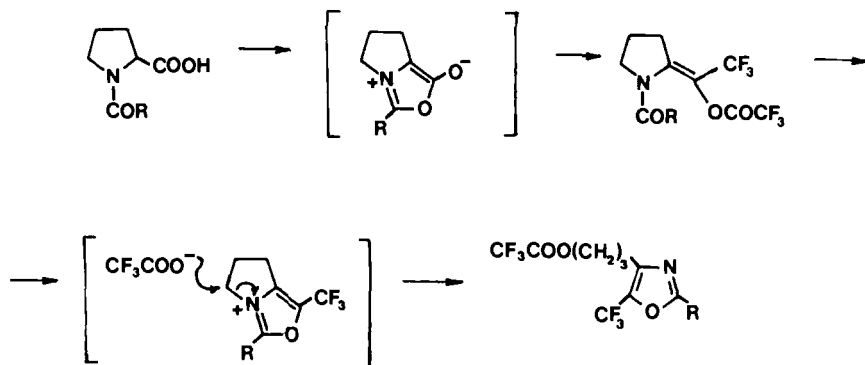


SCHEME 25

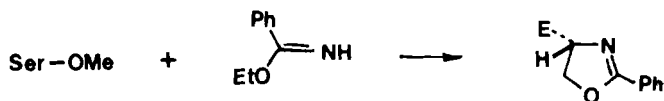
oxazolidinecarboxylate is formed (Scheme 25) (79TL3913). Several related AAs behave similarly.

Other related reactions involve *N*-fluorenylmethyloxycarbonyl (*N*-Fmoc) AAs and aliphatic aldehydes (83JOC77) or *N*-substituted *t*-butoxycarbonyl (*N*-Boc) AAs and 2,2-dimethoxypropane (acetone dimethyl ketal) (84TL5855; 87JOC2361; 88TL2019), as well as *N*-(dimethylthio)methylene derivatives of an AA and aromatic aldehydes [89JCS(P1)1577].

When treated with TFAA in pyridine or in the presence of DMAP, *N*-acylprolines, are transformed into trifluoromethyl oxazoles in good yield. A reaction mechanism involving the mesoionic bicyclic intermediate is postulated (Scheme 26) [93H(36)2441, 93TL859]. Hippuric acid is transformed via a mixed anhydride reaction with ethyl chloroformate into 2-phenyloxazolidin-5-one (86H1325). *N*-Protected L-Phe was cyclized with PCl_5 (77CC281) or thionyl chloride or phosgene [79JCS(P1)3203].



SCHEME 26



SCHEME 27

Reaction of Ser-OMe with benzimino ethyl ester resulted in the formation of an oxazoline without racemization (Scheme 27) (85T2379). After forming an amide with 2-amino-1-phenylethanol, *N*-phthalimido AAs were oxidized with CrO_3 and dehydrated by POCl_3 to give substituted oxazoles (91JHC1241).

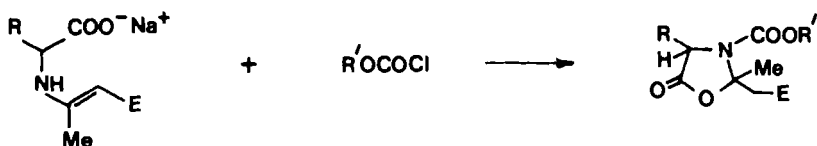
Esters of β -hydroxy- or β -mercapto-AAs react with *n*-butyl isonitrile to give 5-substituted methyloxazoline (or thiazoline)-4-carboxylates in the presence of PdCl_2 as a catalyst (74SC97). The enamine-protected AAs were also transformed into oxazolidin-5-ones after reaction with alkyl chloroformates (Scheme 28) (75S724).

It has been found that AAs do not react with 3,4-disubstituted *o*-benzoquinones in the expected Strecker degradation reaction; instead, a decarboxylative condensation reaction afforded the corresponding benzoxazoles. A mechanistic explanation has been advanced for this transformation. It should be mentioned, however, that other quinones or diones did not react in the described manner (78JOC509).

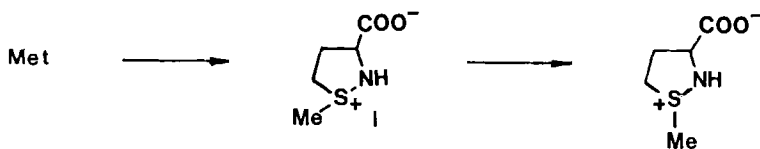
H. ISOTHIAZOLES

There is only one report that describes the oxidation of Met by iodine to give a cyclic iodosulfonium intermediate which is further transformed into *S*-methylisothiazolidine-3-carboxylic acid (Scheme 29) (78JA7121).

A five-membered sultam was prepared from *N,N'*-dibenzoylcystine diethyl ester via a sulfonyl chloride and sulfonamide (Scheme 30) (60CB784).



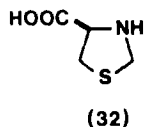
SCHEME 28



SCHEME 29

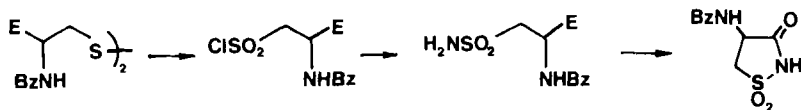
I. THIAZOLES

Most of the reduced thiazole derivatives were obtained from the reaction between L-Cys or its esters with aldehydes or ketones. L-Cystine reacts with formaldehyde at room temperature to give 4(*R*)-thiazolidinecarboxylic acid **32** without racemization [36JBC(114)341; 37JA200; 78JMC1070].

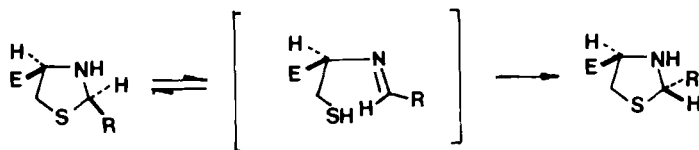


This compound has been found to be a selective drug against human cancer (80N307). L-Cystine was transformed with various aliphatic, aromatic, or heterocyclic aldehydes [48JA1667; 62ZN(B)765; 76JMC1002; 78JMC1070; 82CPB440, 82CPB484; 87LA927] into 2-substituted-4(*R*)-thiazolidine carboxylic acids. For one of them an X-ray analysis was performed (76JA6634). If chiral aldehydes were used, mixtures of two diastereoisomers were obtained. They could be partly resolved by crystallization. NMR measurements have shown that in solution an equilibrium exists between both diastereoisomers and that epimerization occurs by opening of the thiazolidine ring (Scheme 31) (89JHC589). Condensation of L-Cys-OMe with *N*-protected aminoaldehydes and subsequent oxidation with MnO_2 afforded 2-substituted methyl thiazole-4-carboxylates (87JOC1252).

In a total synthesis of D-biotin, the first step involved a condensation of L-Cys with benzaldehyde (75JA5936; 77JA7020). Condensation of Cys with glyoxylic acid gave thiazolidine-2,4-dicarboxylic acid as a mixture of two isomers, formed in an approximate ratio of 7:3, the major product having



SCHEME 30



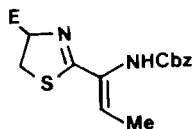
SCHEME 31

the structure of the *trans* isomer (2*S*,4*R*) (94JHC77). Some sugars like L-arabinose (76LA450) or D-galactose (83LA2073) react in a similar manner, and the side chain in the product is a sugar moiety.

N-Formyl Cys undergoes cyclization in a solution of anhydrous hydrogen chloride in glacial acetic acid [68JCS(C)1522], in hydrochloric acid (57E436), or in 10 *M* sulfuric acid (in the case of *N*-acetylcysteine) (61JOC820) to give 2-thiazolidine-4-carboxylic acid or its 2-methyl analog. With ketones like acetone (37JA1690; 58JA1158) or cyclopentanone (49JA1137), the corresponding 2,2-disubstituted 4(*R*)-thiazolidinecarboxylic acids are obtained (48JA1667; 78JMC1070; 82CPB440).

Other reports describe the reaction of Cys-OMe with ethyl acetimidate (61JOC820; 76H1687) or with oxiranecarbonitrile and potassium cyanide. In the last case thiazines are also formed (84TL4295).

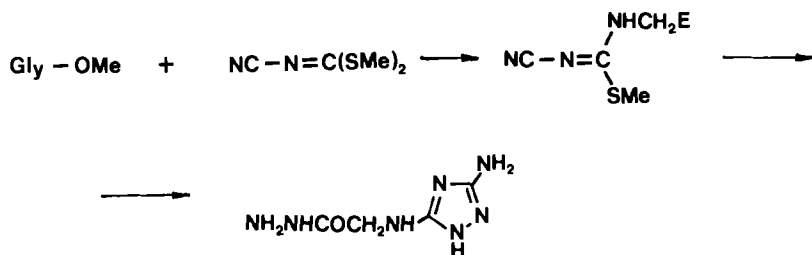
The formation of 2,5,5-trimethylthiazolidine-4-carboxylic acid from an acetaldehyde and D-penicillamine appeared as a detoxication process in ethanol intoxication (78JMC1274; 84JMC591). *N*-Alkoxythiocarbonyl- or benzyldithiocarbonylglycines were also cyclized to the corresponding thiazolin-5-ones (79TL325; 94JHC199). An unsaturated AA, (*Z*)-*N*-Cbz-2-aminobutenoic acid, after being converted into its thioamide, was transformed with ethyl bromopyruvate to give **33**, which is a part of the macrocyclic peptide micrococcin P₁ (92CL1005).



(33)

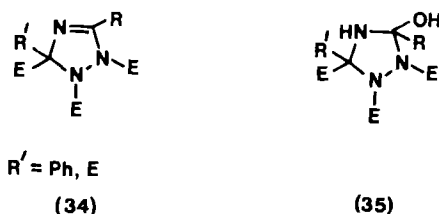
J. FIVE-MEMBERED RINGS WITH MORE THAN TWO HETEROATOMS

Derivatives of 1,2,4-triazoles were obtained from Gly-OEt when condensed with dimethyl cyaniminodithiocarbonic acid and thereafter with hydrazine hydrate (Scheme 32) (71AG886).



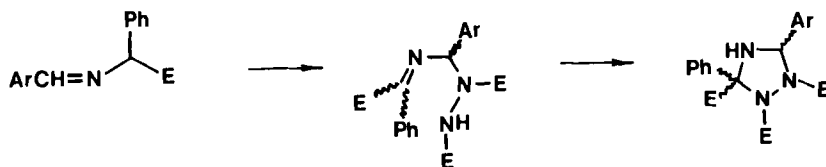
SCHEME 32

Imines of some esters of AAs, such as Val and Phe, undergo dehydration with DEAD to give derivatives of dehydroamino acids. Postulated as intermediates in this transformation, triazolidines were isolated from the same reaction with phenylglycine, which cannot undergo dehydrogenation (Scheme 33) (77CC125). When treated with the Mitsunobu reagent (TPP and DIAD) under various molar ratios esters of *N*-protected phenylglycine or aminomalonate were transformed into **34** and its precursor **35**. In one case a seven-membered heterocycle was formed (88TL4661).

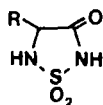


When treated with either sulfur monochloride or thionyl chloride, AAs and 2,3-diaminopropionic acid afforded neither 1,2,5-thiadiazole-3-carboxylic acid or 3-alkyl-4-hydroxy-1,2,5-thiadiazoles in fair to low yields (66JOC1964; 67JOC2823).

N-Protected sulfonamides are formed from AA esters and chlorosulfonyl isocyanate. After deprotection, the product was cyclized in the presence of sodium methoxide or TFA to give **36** (89JOC4471; 91TL6545).

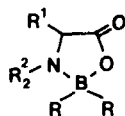


SCHEME 33



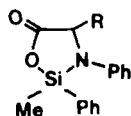
(36)

Various AAs as such or their amidines react with triethylborane, triphenylborane, 9-borabicyclo[3.3.1]nonane (9-BBN), or with KBF_3Ph to give the corresponding boroxazolidones **37**. The reaction has synthetic utility for the simultaneous protection of the α -amino and α -carboxyl groups (83T2995; 93JA11612).



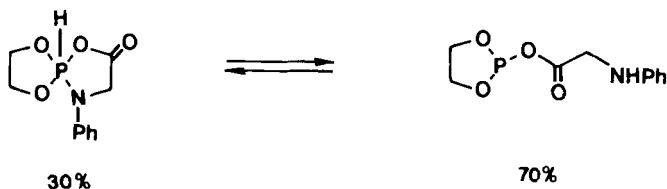
(37)

α -N-Phenyl AAs reacted with some diamidosilanes or methyl phenyl dichlorosilane to give 2-siloxazolidin-5-ones **38** (68JA7255).



(38)

α -Amino acids also react with tricoordinate phosphorus compounds to form spirophosphoranes [72CR(C)(274)1413; 77T635]. Spectroscopic examination revealed that a spiro compound exhibits tautomerism at room temperature and is in equilibrium with the open-ring form (70%) (Scheme 34). This represents an equilibrium of $\text{P(III)} \rightleftharpoons \text{P(V)}$.

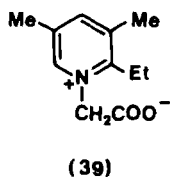


SCHEME 34

V. Six-Membered Rings

A. PYRIDINES

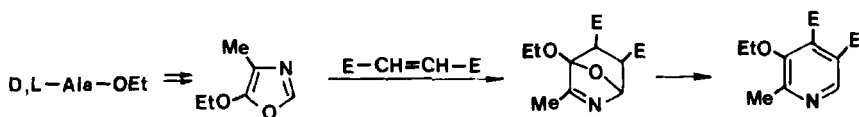
α -Amino acids undergo condensation with alkanals to give pyridinium betaines. For example, Gly gives the betaine **39** with propanal (79JOC1417). The reaction is anticipated to proceed via an unsaturated aldimine. In a total synthesis of pyridoxine from D,L-Ala-OEt, an oxazole derivative is formed; and upon cycloaddition, the adduct decomposes to a pyridine derivative (Scheme 35) (62JOC2705).



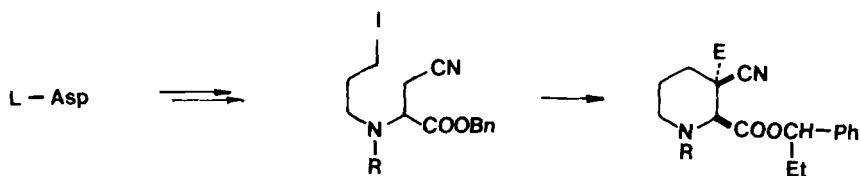
L-Asparagine was used for the synthesis of chiral pipercolates, building blocks for the alkaloid apovincamine. The iodo compound, formed in a multistep transformation from L-asparagine, was cyclized with LDA and ethyl iodide to give the pyridine derivative with a defined configuration (Scheme 36) (85JOC1239).

The cyclic nonproteinogenic AA baikaine, isolated from the wood of a South African tree *Baikaea plurijuga*, was synthesized from L-glutamic acid diethyl ester. In three steps the triester of the tricarboxylic acid was prepared and cyclized with sodium into a 3-pyridone derivative, which in four further steps gave baikaine (Scheme 37) (50JCS3590). Some less efficient syntheses of baikaine starting from either diethyl glutamate or diethyl acetamidomalonate have also been reported (50JCS3590; 58JCS3642; 60JOC489).

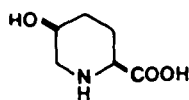
The naturally occurring *cis*-5-hydroxy-L-pipecolic acid **40** was prepared from L-Glu in a stereospecific multistep reaction (88TL2231). Protected L-Glu was transformed into *N*-hydroxycycloornithine **41** in seven steps (94JOC929).



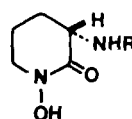
SCHEME 35



SCHEME 36



(40)

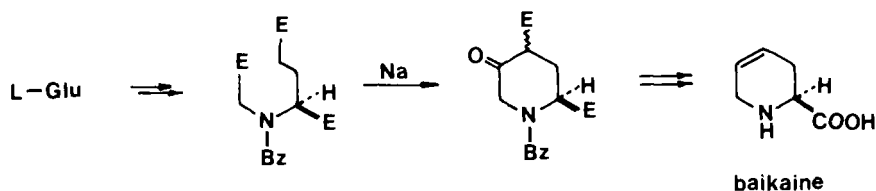


(41)

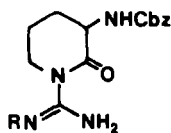
Amino acids with an additional remote amino or carboxylic group are easily transformed into the corresponding lactams. Cyclization is achieved in boiling toluene and in the presence of alumina or silica gel. 3-Amino-2-piperidone is formed from ornithine and a considerable loss of optical activity is observed in the case of L-ornithine (80TL2443; 83LA2021). When treated with nitrosyl chloride, ornithine is transformed into α -chloro- δ -amino-*n*-valeric acid which, upon heating *in vacuo* at 165°C, is transformed into 3-chloro-2-piperidone (25%) together with proline (52JBC587).

Several methods were described for the preparation of pipercolic acid (hexahydropyridine-2-carboxylic acid) from Lys [57ZPC(308)179; 59CCC2318; 75BCJ1341; 81JCS(P1)1769; 82S163; 83CC1169]. In a similar manner, 4-hydroxypipercolic acid was prepared from 5-hydroxy-L-Lys (65JA2030).

It was found that the *N*-protected *p*-nitrophenyl ester of L-Arg spontaneously cyclized into **42** ($R = \text{NO}_2$) (61JOC3347). A related compound **42** ($R = \text{H}$) was obtained as a by-product in the reaction between *N,N*-dicarbobenzoxy-L-Arg and diethyl L-glutamate (59JA2878).



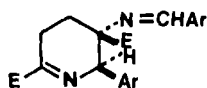
SCHEME 37



(42)

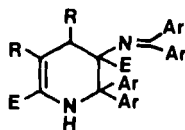
Imines prepared from AAs served as starting materials in cycloaddition reactions. Esters of AAs react with open-chain or cyclic dienes in the presence of formaldehyde to give mixtures of diastereomeric dehydropiperidines or azabicyclo[2.2.1]heptenes and -[2.2.2]octenes (87JOC5746; 88AG307; 89LA231). Iminium salts, obtained with other aliphatic or aromatic aldehydes, react in the same manner (90AG1445; 91LA1045; 92JOC4444). One example of this is the reaction with the Danishefsky diene shown in Scheme 38 (90AG1445).

N-(Arylmethylene)dehydroalanine methyl esters are highly reactive compounds that undergo dimerization, such as [4 + 2]-cycloaddition to give **43** (92T5985). In a similar manner, a small amount of cycloadduct was formed from alkyl 2-(diphenylmethyleneamino)acrylates, prepared from Gly (88S514).

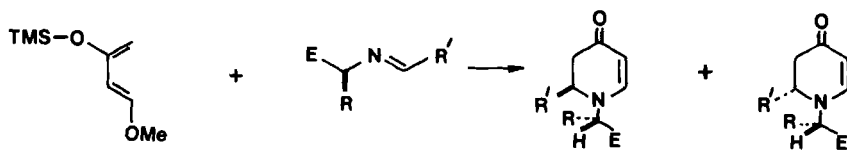


(43)

On the other hand, esters of dehydro α -amino acids dimerize at 145°C in the absence of solvent to give **44** after a [4 + 2]-cyclodimerization and



(44)



SCHEME 38



SCHEME 39

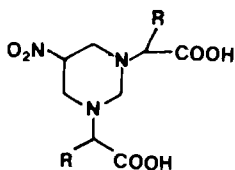
tautomerization (91OPP122). *N*-Protected hydroxy amino acid esters having an alkyl or propargyl group as a terminator cyclize to piperidines—a method that represents a convenient synthesis for 3-ethenyl- or 3-ethenylidene-substituted piperidines (87TL3285). In another reaction, such acids are transformed with formic acid at room temperature into a mixture of diastereoisomeric products (Scheme 39) (91T4039, 91T4063).

When some dihydropyridines were prepared by the Hantzsch one-pot synthesis from alkyl 3-aminocrotonates (85CPB3787), the same type of products were formed by Michael addition of esters of amidinoacetic acid to aralkylidene- β -ketoesters (81AF1173).

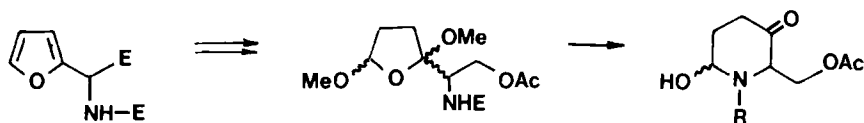
N-Protected 2-furanylglycine ester (prepared from methyl methoxyglycinate) was transformed in several steps into the reduced furan derivative which rearranges in the presence of TFA into an unstable pyridone (Scheme 40) (86TL5085).

B. PYRIMIDINES

Several AAs were transformed into **45** in aqueous solution with formaldehyde and nitromethane after 2–5 weeks (78AP492). The sodium or po-



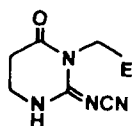
(45)



SCHEME 40

tassium salt of asparagine reacts with either pivaloyl aldehyde or acetone to give derivatives of perhydropyrimidin-4-one-6-carboxylic acid [77JCS(P1)1954; 91JOC1335].

The pyrimidine **46** was obtained from methyl β -alaninate after cyclization with an isourea derivative (90T7803); and when the ester was transformed into the amide and Schiff base was cyclized with benzoic anhydride, the result was a racemic substituted perhydropyrimidin-4-one (91JOC2553).



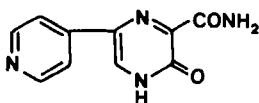
(46)

C. PYRAZINES

Amides of AAs react with 1,2-dicarbonyl compounds in a general synthesis to give the corresponding pyrazinones (49JA78; 52JA1580; 67CB555; 78JHC665).

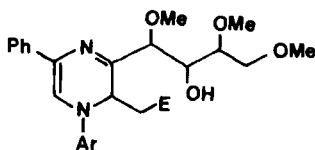
Although the formation of symmetric piperazine-2,5-diones is a well documented transformation (93AHC187), the unsymmetric -ones have been prepared from AAs or their amides with acyl halides, such as pyruvoyl chloride (81RTC73) and α -bromopropionyl bromide (91H923).

Aminomalonamide gave **47** in low yield when condensed with (4-pyridinyl)glyoxal [90H(31)2163]. Similar condensations are reported with methylglyoxal (49JA78) and of glycineamide with phenylglyoxal (78JHC665).



(47)

The reaction that occurs with Gly-OEt, 3,5,6-tri-*O*-methyl-D-glucose, *p*-toluidine, and phenacyl bromide to give **48** (or its regioisomer) represents a particular case (92OPP665).



(48)

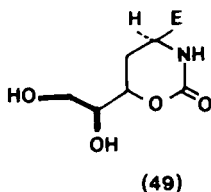
D. PYRONES

2*H*-pyran-2-ones can be prepared from hippuric acid and 1,3-dicarbonyl compounds. Hippuric acid may be transformed first into methyl 2-dimethylaminomethylene-3-benzoylamino propenoate, which then reacts with 1,3-dicarbonyl compounds (90S70); or, in an one-pot synthesis, a mixture of hippuric acid, a one-carbon synthon [*N,N*-dimethylformamide–dimethyl acetal (DMF–DMA), triethylorthoformate (TOF), or diethoxymethyl acetate (DEMA)], and a 1,3-dicarbonyl compound may be heated under reflux in acetic anhydride (89SC1713; 90T2081).

E. OXAZINES

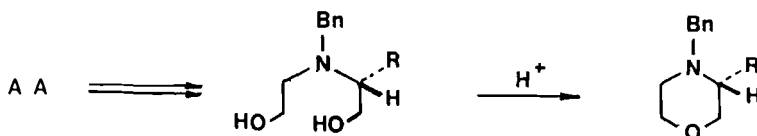
1,3-Oxazine derivatives are formed from unsaturated AAs. Vinylglycine, after epoxidation at the double bond, yielded methyl 1,3-oxazin-2-one-4-carboxylate after treatment with sodium methoxide or *p*-chlorophenol (90TL2291). Similarly, some alkenes react with methyl α -methoxyhippurate and cyclization occurs with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (75TL3737). In sulfuric acid butyrolactones are formed.

When a nonproteinogenic unsaturated amino acid was subjected to the Sharpless asymmetric epoxidation, **49** was formed (87TL3605). It is known that AAs are converted with phosgene into *N*-carboxy- α -amino acid anhydride (NCA) derivatives. Unexpectedly, *N*-protected dehydroaspartic acid gave 1,3-oxazine-2,6-dione-4-carboxylic acid under such conditions (88CL1473).



Optically pure 2,3-dihydro-6*H*-1,4-oxazin-2-ones were prepared in a two-step reaction from *N*-protected AAs and α -bromoketones (78JOC135). When heated in boiling toluene and HCl 2,2-dimethylamino acid amides were transformed into the corresponding 3,3-dimethyl-1,4-oxazine-2,5-diones (83TL1921; 87HCA329).

Reduction of the carboxylic group of an AA and subsequent treatment with ethylene oxide afforded a dihydroxy derivative that cyclized in 70% sulfuric acid. From L-AAs morpholines with the (*R*)-configuration at the chiral center were obtained (Scheme 41) (80T409). Esters of AAs, after



SCHEME 41

being alkylated with prop-2-ynyl bromide, underwent mercury-catalyzed cyclization into a mixture of 2,3-dihydro-1,4-oxazin-2-ones and 6-methylene-2-morpholinones in various ratios. With optically active AAs, racemization takes place (82S850).

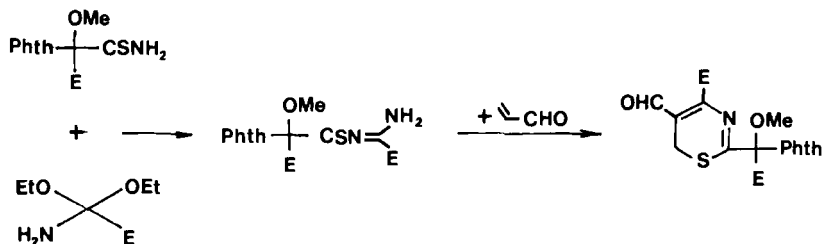
F. THIAZINES

L-Perhydro-1,4-thiazine-3-carboxylic acid 1-oxide is a natural AA found in some red and brown algae. It was synthesized from L-cystine in several steps. The heterocyclic ring was prepared by cyclization of *S*-(2-chloro- or bromoethyl)-L-Cys in the presence of triethylamine. Perhydro-1,4-thiazine-3-carboxylic acid was then oxidized with $\text{H}_2\text{O}_2/\text{AcOH}$ to give the sulfoxide (64JOC2203). Cystine also reacted with ethyl α -bromopropionate in liquid ammonia to give 5-oxoperhydro-1,4-thiazine-3-carboxylic acid [76JCS(P2)203].

For the preparation of cepheids from a protected *t*-butyl α -methoxyglycinate thioamide and an orthoamide, an azathiadiene was formed which afforded the 1,3-thiazine derivative after cycloaddition of acrolein (Scheme 42) (89JOC2889).

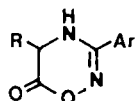
G. SIX-MEMBERED RINGS WITH THREE HETEROATOMS

1,2,4-Triazines are formed from AAs after being transformed with DMF-DMA into amidines and subsequent treatment with hydrazine [90H(30)393]. Esters of heterocyclic dehydroamino acids reacted in a similar



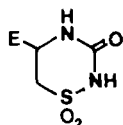
SCHEME 42

manner (94JOC507). *N*-Acylated ethyl esters of AAs, after being thionated into thioacyl derivatives, yielded 1,2,4-triazin-6-one derivatives (83T3419). 1,2,4-Triazin-6-ones were also obtained from AAs and nitrile imines generated *in situ* from hydrazonoyl chlorides (91H1879). The reaction with nitrile oxides, however, yielded derivatives 1,2,4-oxadiazine **50** at low temperature (84JHC455).



(50)

Ethyl sulfonamidomethylglycinate was prepared from L-cystine in several steps; it was then transformed with 1,1'-carbonyldiimidazole into thiadiazine derivative **51** (84JMC228).



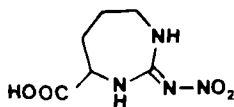
(51)

VI. Seven-Membered Rings

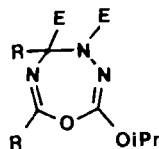
If AAs are heated in acetic anhydride in the presence of 1,2-dicyanocyclobutene as a dipolarophile, 4,5-dihydroazepines are formed in good yields. For example, the reaction with Ala is actually considered a cycloaddition of the intermediate mesoionic derivative (Scheme 43) (80JHC1593).

Lysine and its derivatives are used for the preparation of ϵ -caprolactams. From L-Lys or its ester, (*S*)-3-aminoheptahydro-2*H*-azepin-2-one is prepared (43JCS39; 57JCS4830; 78S614; 79JOC4841; 80TL2443).

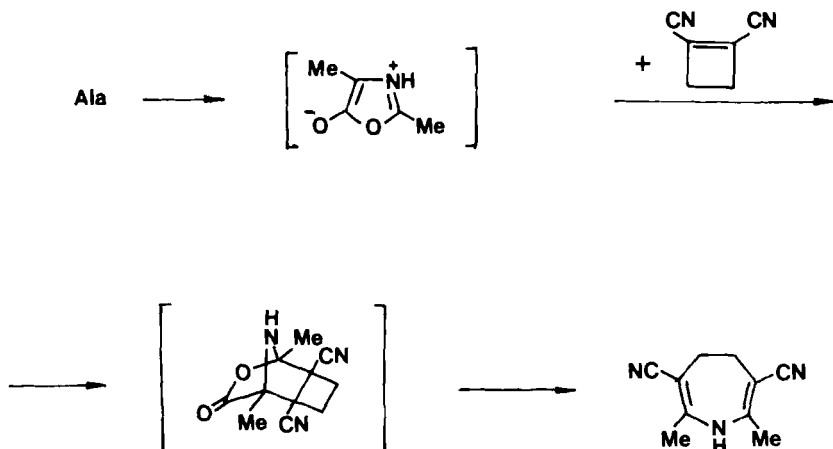
When nitro-L-Arg and a solution of sodium carbonate were heated, the AA cyclized into **52** (61JOC3347).



(52)



(53)



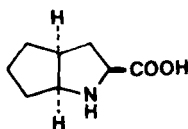
SCHEME 43

The reaction of *N*-protected aminomalonate with the Mitsunobu reagent (TPP and DIAD) gave a mixture of a triazoline as the main product and **53** (31%). This compound was formed by the attack of the azodicarboxylate oxygen rather than nitrogen during the cyclization step (88TL4661).

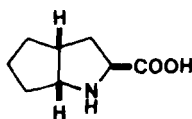
VII. Bicyclic 5-5 Ring Systems

A. ONE HETEROATOM ADJACENT TO THE RING JUNCTION

Treatment of *L*-Ser-OMe with 3-bromocyclopentene after the hydroxy group was replaced with iodide gave in the presence of 2,2'-azobisisobutyronitrile (AIBN) and tri-*n*-butyltin hydride a mixture of stereoisomers. These stereoisomers were separated and transformed into (1*S*,3*S*,5*S*)-**54** and (1*R*,3*S*,5*R*)-isomer **55**, which are precursors of the potent angiotensin-converting enzyme inhibitors [89H(28)957]. Isomer **54** was also obtained from *N*-acetylserine methyl ester which was converted into its chloro analog and reacted with cyclopentenepyrrolidine (84TL4479).

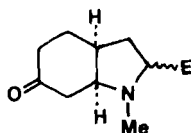


(54)



(55)

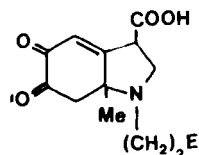
Anodic oxidation of halogenated tyrosines was studied in connection with some sponge metabolites (cavernicolin model compounds). The methyl ester of 3,5-dibromotyrosine afforded four different products in a 41:10:26:23 ratio with 23% overall yield as a result of equilibration. (Scheme 44) [93JCS(P2)3117]. A related compound was obtained as a mixture of stereoisomers **56** from a Diels–Alder reaction between *N*-acetyldehydroalanine methyl ester and 1-methoxy-1,3-cyclohexadiene (87TL2371).



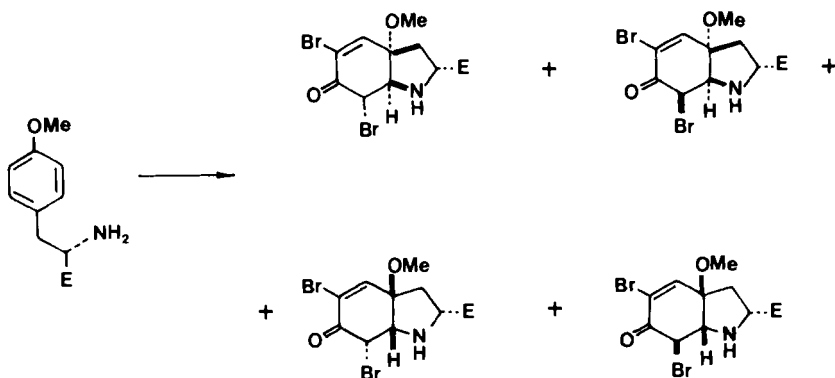
(56)

Protected L-Asp reacted with cyclohexyl bromide and was converted into an *N*-hydroxy-2-thiopyridone derivative. Photolysis at room temperature afforded a mixture of cyclic stereoisomers (Scheme 45), the stereochemistry of which was determined by NMR and X-ray analysis (87TL1413).

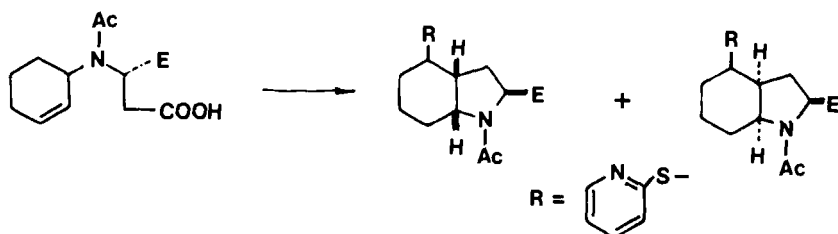
Oxidation of 4-methoxycatechol with Ag_2O in the presence of β -alanine methyl ester resulted in the formation of a complex mixture from which compound **57** was isolated in 0.4% yield (82HCA1279).



(57)



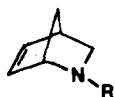
SCHEME 44



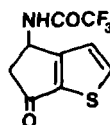
SCHEME 45

When treated with formaldehyde, esters of AAs form immonium ions which undergo reaction with cyclopentadiene to give 2-azanorbornenes **58**. Decomposition of **58** afforded esters of *N*-methylamino acids without racemization (87JOC5746).

A heterocyclic amino acid, 3-amino-3-(3'-thienyl)propionic acid, when treated with TFA and TFAA, is transformed under severe reaction conditions into compound **59** (86TL2607).



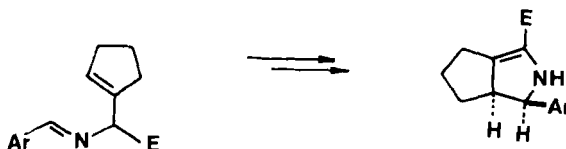
(58)



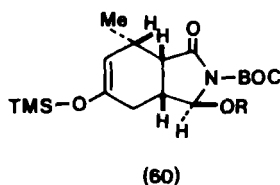
(59)

B. ONE HETEROATOM NOT ADJACENT TO THE RING JUNCTION

When transformed into vinillogous imines, AAs undergo stereospecific 1,5-electrocyclization (Scheme 46) (83TL1201). In connection with the structural studies of domoic acid, a compound from a marine organism having high neurotransmitting activity, the bicyclic system **60** was prepared from *N*-protected L-pyroglutamic acid. The key step was a [4 + 2]-cycloaddition to the give compound as a single stereoisomer (82JA3511).

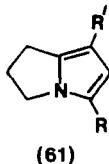


SCHEME 46



C. SYSTEMS WITH ONE HETEROATOM AT A RING JUNCTION

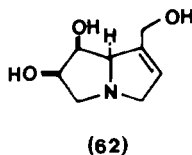
As a first example of a 1,3-dipolar cycloaddition, *N*-formylproline reacted with propargylic aldehyde to give compound **61a**. This is a one-step preparation of a pheromone, isolated from *Danaus affinis* and *Uthethesia lotrix* [78CI(L)349]. The 1-carbethoxy analog was prepared in a similar manner from *N*-formylproline and ethyl propiolate (74JOC731). Natural 4-hydroxy-L-proline and its *N,O*-diformyl derivative undergo regiospecific 1,3-dipolar cycloaddition of ethyl propiolate to give analogs of **61a**. The products were used in the synthesis of some pyrrolizidine alkaloids such as laburnine, isoretronecanol, and supinidine [79CC1181; 81JCS(P1)909].



a: R = H, R' = CHO

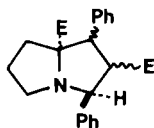
b: R = 2-pyridyl, R' = CN

(2*S*,4*R*)-4-Hydroxyproline also served as starting material for the preparation of crotanecine, isolated from alkaloids of *Crotalaria* sp. Compound **62** was obtained in fifteen steps in 4% overall yield (84H2735).



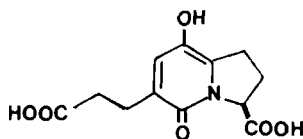
Also, in the form of *N*-(2-pyridylcarbonyl)proline Pro undergoes 1,3-dipolar cycloaddition with 2-chloroacrylonitrile to give two tetracyclic products and **61b** in 5% yield (85TL5447). When Pro-OMe was heated with methyl cinnamate and benzaldehyde in toluene for several hours, two iso-

meric compounds **63** were formed (85TL2775). Similar results were obtained with *N*-phenylthiomethylproline methyl ester (84TL1579).



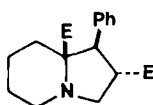
(63)

An angiotensin-converting enzyme inhibitor **64** was prepared in several steps from *L*-pyroglutamic acid. The formation of the bicyclic system was achieved with methylene glutaric anhydride (89TL3621).

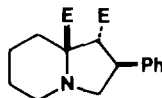


(64)

N-Phenylthiomethylpipecolic acid methyl ester afforded with methyl cinnamate and a mixture of two regioisomers **65** and **66** (84TL1579). Pipecolic acid and diethyl fumarate or maleinate gave three isomers (85TL2775).

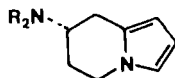


(65)



(66)

After reduction and reaction with 2,5-dimethoxytetrahydrofuran, *L*-Asparagine was converted into a pyrrole derivative which was cyclized with trifluorosulfonyl anhydride into **67** [90H(31)9].



(67)

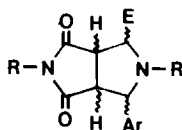
The alkaloid tylophorine was synthesized from ornithine. Ornithine was first converted into 1-pyrroline which gave the alkaloid septicine **68** after several transformation steps. This alkaloid was then oxidized into tylophorine [82JCS(P1)2477].



D. SYSTEMS WITH TWO HETEROATOMS

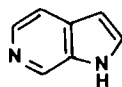
1. One Heteroatom in Each Ring

Compounds of the general formula **69** are prepared by cycloaddition of *N*-methyl- or *N*-arylmaleimides with arylidene imines of AAs and in the presence of an aromatic aldehyde. Stabilized azomethine ylides are formed as intermediates, which then afford the cycloadducts. Several isomers are formed, and the influence of various metal salts and solvents was investigated (87BCJ4067; 88T557). Similar transformations have been performed with *N*-allyl glycine esters (91TL1359).



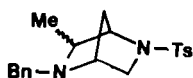
(69)

Condensation of *N*-protected pyrrole-2-carboxaldehyde with ethyl α -amino- β,β -diethoxypropionate followed by reduction and cyclization in the presence of TiCl_4 afforded the pyrrolo[2,3-*c*]pyridine derivative **70** in excellent yield (93T8139).

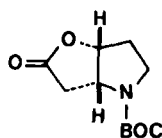


(70)

Derivatives of the 2,5-diazabicyclo[2.2.1]heptaine ring system (bridged piperazines) have been prepared from 4-hydroxyprolines. In a multistep transformation from *trans*-4-hydroxy-L-proline (the last step was cyclization with benzylamine) a mixture of diastereoisomers **71** was obtained and separated [92H(34)241]. In a similar manner, the methyl and oxo analogs were obtained [67AJC1493; 92H(34)679]. The commercially available *N*-



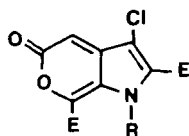
(71)



(72)

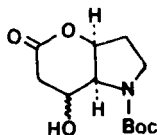
Cbz-4-hydroxy-L-proline was used in the preparation of **72** (the Geissman-Waiss lactone), which is a synthon for necines (82H23). This compound was prepared in eight steps (62JOC139). The alkaloids retronecine, platynecine, and croalbinecine were prepared from the lactone (83H1331).

When chlorinated and dehalogenated in the presence of a base, dimethyl *N*-acetylstizobolate, a derivative of the nonproteinogenic stizolobic acid, afforded a derivative of the pyrrolo[3,4-*b*]pyran system **73** (86LA1968).



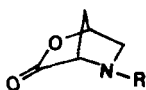
(73)

Two syntheses of the pyrrole derivative detoxinine and a part of the natural depsipeptide detoxin are described. In each, the formation of detoxinine takes place from bicyclic system **74**, obtained in a multistep transformation from *N*-protected 3-hydroxy- or 4-iodoproline (83LA982; 90CC1240).



(74)

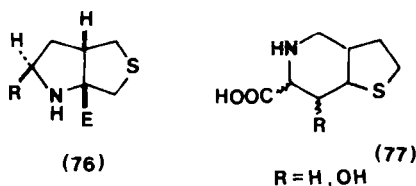
N-Protected 5-aza-2-oxabicyclo[2.2.1]heptanes and their oxo analogs are usually prepared from 4-hydroxyproline or its derivatives in several steps [57JA185; 71JHC53, 71N(L)(230)457, 71T961]; however, **75** was obtained in a facile one-step transformation involving intramolecular dehydration



(75)

(83H817). A pheromone exobrevicomin was synthesized in a multistep reaction sequence from L-Glu (85CC83).

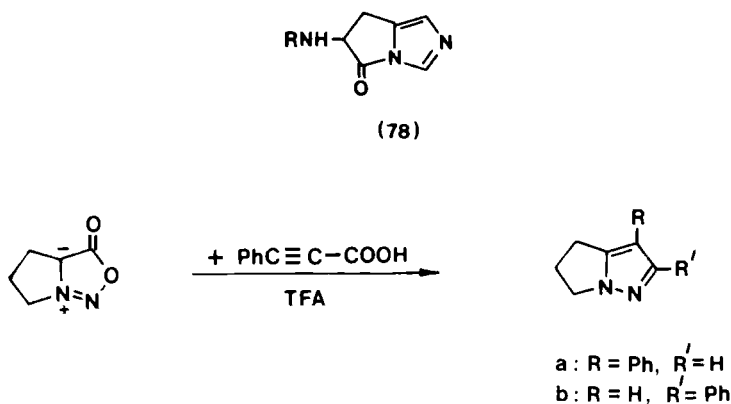
From *S*-allyl-L-Cys and pyridoxal, an imine was formed which reacted as a 1,3-dipole and was transformed into **76** by an intramolecular cyclization (89T7581). From β -thienylalanine or β -thienylserine, substituted tetrahydrothieno[3,2-*c*]pyridines **77** were prepared. For cyclization, either formaldehyde or Gly in the form of cupric glycinate were used (81H35; 82H1797).



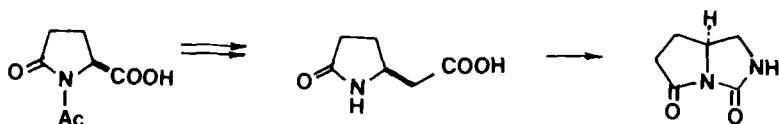
2. One Heteroatom at a Ring Junction

The mesoionic compound prepared from L-Pro (83TL1067) reacts with acetylenic compounds to give pyrrolo[1,2-*a*]pyrazoles after extrusion of carbon dioxide (Scheme 47). With phenylpropionic acid, the natural product withasomnine (**a**) was formed in low yield (7%) together with its regioisomer (**b**, 5%) (85TL5739).

From (*S*)-1-acetylpyroglutamic acid via its chloride and subsequent reaction with diazoketone, the homologous ester was obtained. Hydrolysis gave the acid, which reacted with DPPA and afforded the optically active product (Scheme 48) [92H(33)619]. In a similar manner, compound **78** was obtained from *N*-protected L-Hys with *N,N'*-diisopropylcarbodiimide (59JA6086).

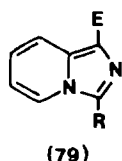


SCHEME 47

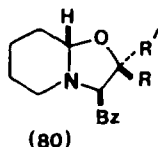


SCHEME 48

Compound **79** and its 3-methyl analog were prepared from ethyl α -(2-pyridyl)glycinate with DMF-DMA, TOF, or DEMA [91JHC1715, 91ZN(B)1110].



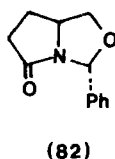
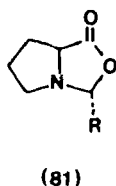
Derivatives of the pyrrolooxazole were obtained either from Pro after reaction with phenylglyoxal to give a mixture of isomers **80** (87TL6077) or from a pyroglutamic acid derivative [89H(29)2089].

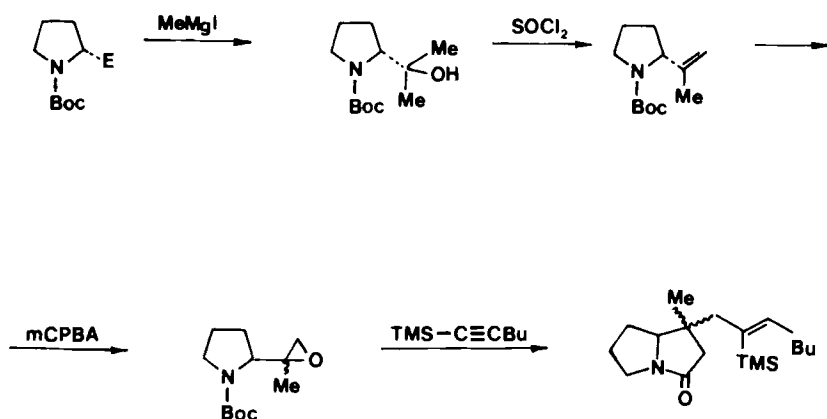


a: $R = H, R' = Bz$

b: $R = Bz, R' = H$

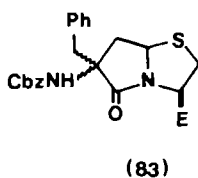
In connection with the enantioselective alkylation of Pro or 4-hydroxyproline, the azabicyclo[3.3.0]octane system **81** was obtained after reaction with pivaldehyde (81HCA2704; 85HCA155). In a more complex transformation *N*-protected L-Pro was transformed into the same bicyclic system (Scheme 49) (81JA1851; 84JA4192). The product was prepared as a model substance in the total synthesis of pumiliotoxin. A related compound **82** was prepared from 5-(hydroxymethyl)-2-pyrrolidinone (prepared from L-pyroglutamic acid) by an acid-catalyzed condensation with benzaldehyde (86JOC3140).





SCHEME 49

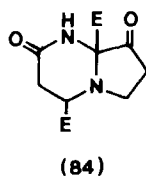
Reaction between D-Cys and an oxazoline aldehyde, prepared from L-Phe gave the bicyclic compound **83** [92H(34)903]. A derivative of the same system was obtained from penicillamine with a functionalized AA (88CC1128).

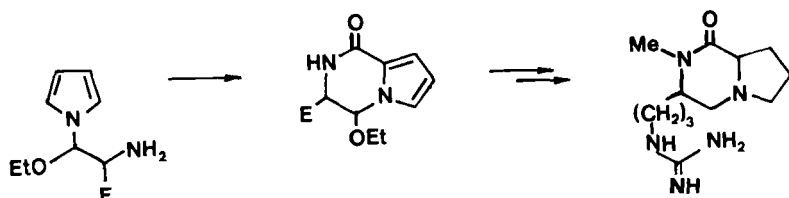


VIII. Bicyclic 5-6 and 5-7 Ring Systems

Methyl 2-pyrrole carboxylate was transformed in two steps into an *N*-pyrrolylalanine derivative which was converted into a pyrrolo[1,2-*a*]pyrazine after heating under reflux in toluene. Five subsequent steps led to peramine (Scheme 50), a principal insect feeding deterrent, from *Acremonium iolli* (88CC978).

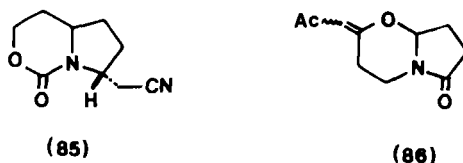
A derivative of the related pyrrolo[1,2-*a*]pyrimidine system **84** was prepared from L-asparagine via a hydroxypyrrolidine (92JOC2641).



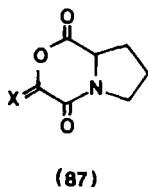


SCHEME 50

In the synthesis of the alkaloid gephyrotoxin, *L*-pyroglutamic acid was used as a starting material for the preparation of intermediate **85** (81TL4197). A related pyrrolooxazine **86** was also obtained from pyroglutamic acid after *N*-substitution and ring closure in the presence of silica

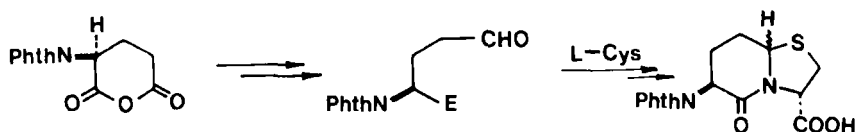


gel [89H(29)2089]. When treated with a large excess of oxalyl chloride, *L*-Pro afforded **87a**, which was regarded as “*L*-proline-*N*-oxalic anhydride” (67JOC4072).



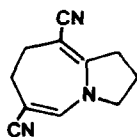
a: X = O
b: X = R, H

N-Phthalyl-*L*-glutamic anhydride was converted in four steps into an aldehyde which reacted with Cys to give a thiazolopyridine derivative after cyclization (Scheme 51) (85TL647).

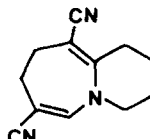


SCHEME 51

As in the case of the formation of an azepine (Scheme 43), Pro afforded a pyrrolo[1,2-*a*]azepine **88**, and pipecolic acid afforded a pyrido[1,2-*a*]azepine **89** (80JHC1593).

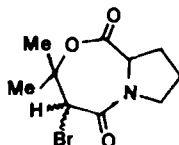


(88)

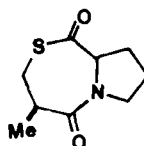


(89)

The reaction between unsaturated acids and Pro afforded the acylprolines, which were cyclized to the corresponding pyrrolo[2,1-*c*]oxazines **87b** (79T2337, 79T2345). From an *N*-(β -methylcrotonyl)proline the corresponding pyrrolo[2,1-*c*][1,4]oxazepines **90** were formed (79T2345). A pyrrolo[2,1-*c*][1,4]thiazepine derivative was synthesized from L-Pro in a multistep reaction sequence. Compound **91** is an orally active angiotensin-converting enzyme inhibitor (80JHC1647).



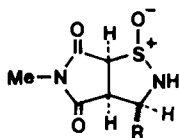
(90)



(91)

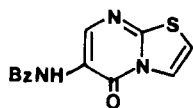
IX. Bicyclic 5-5 and 5-6 Ring Systems with Three Heteroatoms

When L-AAs are treated with *N*-sulfonylaniline (PhNSO) and *N*-methylmaleimide, cycloadducts are formed. The reaction is stereospecific, giving only one stereoisomer **92**, whereas with esters of AAs a mixture of diastereoisomers is formed (88T4941).

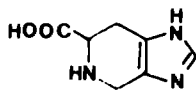


(92)

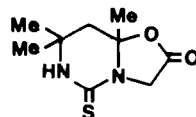
A one-pot synthesis of thiazolo[2,3-*b*]pyrimidines **93** was developed. Compounds of this system were synthesized from cyclic protected glycines (oxazolinones) and 2-aminothiazole (81H2149). A derivative of tetrahydroimidazo[2,3-*c*]pyridine **94** was formed from His and formaldehyde (44BJ309). Glycine reacts with 4-isothiocyanato-4-methylpentan-2-one to give **95**, a derivative of oxazolo[3,2-*c*]pyrimidine (87T2177). With the related isothiocyanate, which has one methylene group less, only an imidazolinethione derivative is formed.



(93)



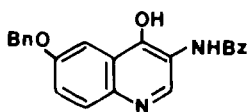
(94)



(95)

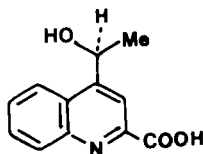
X. Quinolines and Isoquinolines

Just a few quinoline derivatives have been prepared from AAs. Upon condensation with *p*-benzyloxyaniline, ethyl formylhippurate yielded the 4-hydroxyquinoline **96** after some transformations (82JMC501).



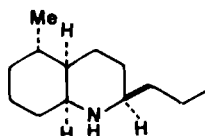
(96)

For biosynthetic studies of the formation of the macrocyclic peptide antibiotic thiostrepton, isotopically labeled [^{13}C]-AAs were employed. The quinaldic acid moiety **97** of this antibiotic was shown to be biosynthesized from 3-methyltryptophan, and a mechanism has been proposed (93JA7992).



(97)

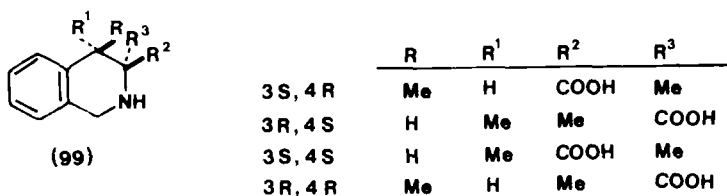
An enantioselective synthesis of the natural venom pumiliotoxin C **98** and its unnatural enantiomer was achieved from (*R*)-norvaline in a multistep



(98)

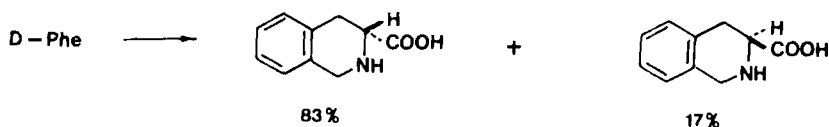
sequence. The (*S*)-isomer of **98** was prepared from (*S*)-norvaline (77HCA204).

Phenylalanine, its *N*-benzoyl derivative, and ring-substituted phenylalanines undergo a Pictet–Spengler reaction with formaldehyde or acetaldehyde in the presence of a mineral acid to give the corresponding tetrahydroisoquinolines [11CB2030; 46JCS617; 48JA180; 51JOC430; 92H(34)757]. Although it was previously anticipated that no racemization would occur during this reaction, it was later found that some racemization occurred during the conversion of *D*-Phe to give *D*- and *L*-carboxy derivatives in a ratio of 83:17 (Scheme 52). The *L*-isomer was obtained from the *L*-AA with 99% enantiomeric purity (88JMC2092). All four diastereoisomeric α,β -dimethylphenylalanines have been converted under the Pictet–Spengler reaction conditions into four stereoisomers **99**. Under normal conditions



the (3*S*,4*R*) and (3*R*,4*S*) isomers were obtained. The other two isomers were obtained as *N*-methyl derivatives. This side reaction could be suppressed under modified conditions by using paraformaldehyde and performing the reaction in a sealed tube at an elevated temperature. As a consequence, the other two isomers (3*S*,4*S*) and (3*R*,4*R*) were obtained in high yield (94JOC1789).

L-DOPA [3-(3,4-dihydroxyphenyl)alanine] and its two mono *O*-methyl ethers gave the corresponding tetrahydroisoquinolines with formaldehyde and acetaldehyde. With acetaldehyde, *L*-DOPA gave a 95:5 mixture of



SCHEME 52

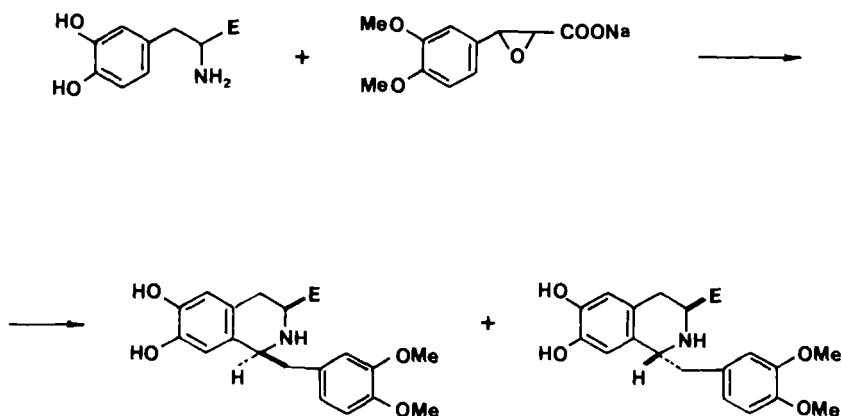
isomers whose main isomer was the 1-*cis* acid, as shown by X-ray analysis. Similar results were obtained with the corresponding *O*-methyl ethers of L-DOPA (72HCA15). The same reaction was used to prepare (*S*)- or (*R*)-laudanoline (72TL2215; 74CPB2614; 75CPB1025; 77CPB69) and (*S*)-reticuline (75CPB1063).

α -Amino acids can participate as the amine component in a Mannich reaction with either ketones or phenols. In the latter case, the Mannich bases can be cyclized with sulfuric acid to 1,2-dihydro-4(3*H*)isoquinolones (75JHC869).

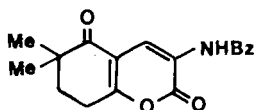
3-(3,4-Dihydroxyphenyl)alanine and its monobenzylated methyl ester were transformed with a glycidate into isoquinoline derivatives, which are used as building blocks for the synthesis of the alkaloids laudanoline and reticuline (75CPB1025, 75CPB1063). The transformation gave a mixture of diastereoisomers, the 3-*cis* isomer being the major product (Scheme 53).

XI. Benzopyrones

Three synthetic approaches for benzopyrones have been developed that use Gly as starting material. Hippuric acid was transformed with acetic anhydride into 2-phenyl-5(4*H*)oxazolone or further into its 4-ethoxymethylene derivative, then reacted with cyclic 1,3-dicarbonyl compounds (such as like dimedone) to form **100** [90LA501; 92H(33)843]. On the other hand, when hippuric acid was transformed into methyl 2-benzoylamino-3-dimethylaminopropenoate, it reacted with resorcinol to give a 7-hydroxybenzopyrone derivative (89JHC1273).



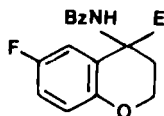
SCHEME 53



(100)

1,4-Benzoquinone reacted with dialkyl aminocrotonate to give 3-amino-4-carbalkoxy-6-hydroxycoumarin (90JHC1447).

From diethyl acetamidomalonate and 2-(4-fluorophenoxy)ethyl bromide a spiro-benzopyranyl amino acid **101** could be prepared (88TL5493).

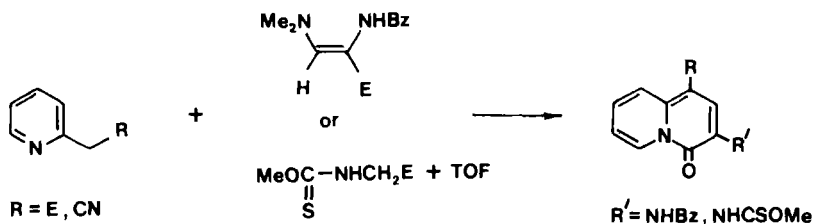


(101)

XII. Other Fused Bicyclic 6-6 and 6-7 Rings

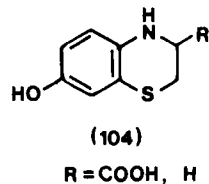
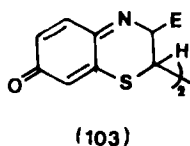
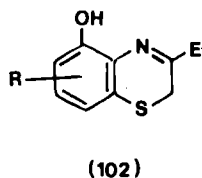
2-Benzoylamino-3-dimethylaminopropenoate reacts with methyl 2-pyridylacetate or 2-cyanomethylpyridine to give derivatives of the pyrido [1,2-*a*]pyridine system. Alternatively, this ring system is also formed with ethyl *N*-methoxythiocarbonylglycine and TOF (Scheme 54) (94JHC125).

α -Amino acids react with *o*- and *p*-quinones. With aminochrome and dopamine after oxidation to the *o*-quinone, L-Cys gives the corresponding 1,4-benzothiazine-3-carboxylic acid derivatives **102** (74T3627; 94JMC1084). The reaction of Cys with quinones is important in the biological process of the biosynthesis of luciferin and sulfur-containing phaeomelanins and trichochromes found in red hair and feathers. Compound **103** was obtained by heating Cys-OEt and *p*-benzoquinone in water (75CC42, 75CC492). Subsequent experiments have confirmed the incorporation of *p*-benzoquinone into luciferin (76CC32). When this reaction was reexamined in the



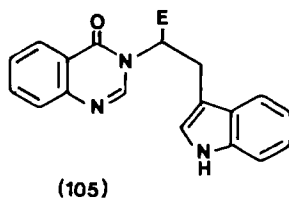
SCHEME 54

absence of air, it was found that it gives a heptacyclic trimer as a major product and a small amount of a related tetramer. If NaBH_4 was added after 1 min, the acid **104** and its decarboxylated product were isolated (88T6447).

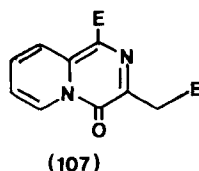
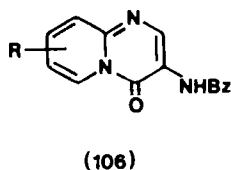


Compound **105** was prepared in several steps from Trp. It was further converted into tryptiquivaline, a toxic metabolite from *Aspergillus fumigatus* (79JA5084; 83JA3709; 84TL3865; 84H224).

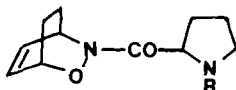
It is well known that isothiocyanates react with α -AAs to give hydantoin, but methyl *o*-isothiocyanatobenzoate gives a tetrahydroquinazoline derivative (67HCA1440).



A one-pot synthesis of pyrido[1,2-*a*]pyrimidines **106** from protected glycines (oxazolinones) and 2-aminopyridines was developed (81H2149). Another approach used methylazines which were treated with DMF-DMA, then the enamines that formed were treated with protected glycine. In addition to the above-mentioned bicyclic system, several related condensed bicyclic systems with a ring-junction nitrogen were prepared (90JHC359; 91BSB533). Compound **107** was prepared in a similar manner from ethyl α -(2-pyridyl)glycinate and DMAD (93JHC1253).



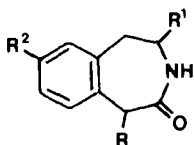
After being converted into the hydroxamic acid, *N*-protected L-Pro was transformed in situ into the acylnitroso dienophile, which underwent cycloaddition with cyclohexadiene to give the bicyclic cycloadduct **108** (or its mirror image) (89TL7061).



(108)

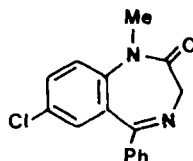
Several condensed 6-7 bicyclic systems have been prepared from AAs. Some *N*-chloroacetylated AAs are photochemically transformed into heterocycles with a condensed seven-membered ring. For example, *N*-chloroacetyl-D,L-*m*-tyrosine is easily cyclized into benzazepinone **109a** on irradiation with a high-pressure mercury lamp (67JA1039; 68JA776).

When acylated with (bismethoxycarbonylamino)acetyl chloride, D,L-Phe cyclized with concentrated sulfuric acid to benzazepinone **109b** (87T439). Also of importance are the preparations of 1,4-benzodiazepines from 2-aminobenzophenones and AAs or their esters. The tranquilizer diazepam (Valium) **110** is prepared from Gly-OEt. If optically active AAs are used, chiral products are obtained [73JHC591; 92H(33)235]. In other synthetic approaches, *o*-nitrobenzoylglycines are used as a starting material or esters of AAs are treated with isatoic anhydride (66JMC6; 75JHC1323).



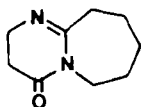
- a: R = H, R¹ = COOH, R² = OH
b: R = NHE, R¹ = E, R² = H

(109)

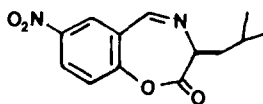


(110)

α -Amino acids also react with cyclic lactim ethers to give first *N*-substituted AAs which are transformed, for example, into **111** (59LA166). L-Leucine is transformed with 5-nitrosalicylaldehyde into a benzoxazepinone **112** (73USP3704246).

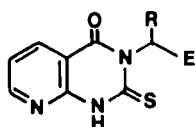


(111)

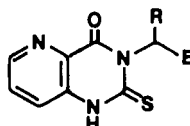


(112)

Some condensed 6-6 heterocyclic systems with three or more heteroatoms have been generated from AAs. Derivatives of the pyrido[2,3-*d*]- or pyrido[3,2-*d*]pyrimidine systems **113** and **114** were prepared from 3-(or 2-)ethoxycarbonyl-2-(or 3-)isothiocyanatopyridine and AAs (90JHC413, 90JHC643).

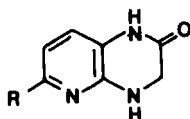


(113)



(114)

Derivatives of pyrido[2,3-*b*]pyrazine were prepared from pyridyl-substituted AAs. Reductive cyclization afforded **115** (79CZ387), whereas cyclization with potassium carbonate gave the dione **116** (87TL6363).

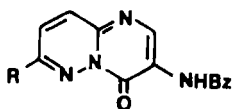


(115)



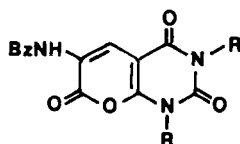
(116)

When treated with the reaction product of hippuric acid and DMF-DMA, 3-aminopyridazine was transformed into a derivative of the pyridazino-pyrimidine system **117**. The same result was achieved when 3-aminopyridazine was reacted first with DMF-DMA and thereafter with the protected cyclic glycine derivative (88H903; 90JHC359).



(117)

Methyl 2-benzoylamino-3-dimethylaminopropenoate reacts with barbituric acid or its 1,3-dimethyl derivative to give a pyranopyrimidine **118** (89JHC1273).



(118)

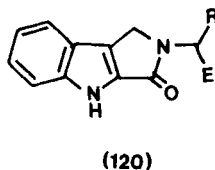
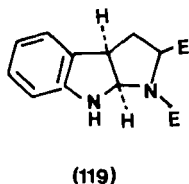
A mixture of Gly, L-Ala, L-Val, L-Lys, L-Asp, and L-Glu was heated without a solvent at 160–200°C, thereby simulating prebiotic conditions. Several tricyclic heterocycles and a pteridine derivative were isolated from the reaction mixture (79AG510).

XIII. Tricyclic and Polycyclic Ring Systems

A. PYRROLOINDOLES

Tryptophan and its derivatives can be characterized as existing in three possible tautomers: the indole form, the indolenine form (hydrogen atom at position 3), and the cyclic form. In neutral solvents only the indole form exists; NMR studies indicate no evidence for the other two isomers (60JA2184). However, when dissolved in 85% phosphoric acid or TFA, *N*-methoxycarbonyltryptophan exists as a pyrrolo[2,3-*b*]indole derivative **119** (78JA5564; 81T1487). Although the tricyclic compound is stable in the crystalline form, it reverts to the starting material when it dissolves in acetic acid or methanolic HCl.

A derivative of the isomeric system, **120**, is formed if AA esters are condensed with 2-carbalkoxy-3-formylindole under reducing conditions (90JOC1390).



B. TETRAHYDRO- β -CARBOLINES

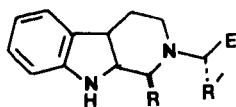
The formation of tetrahydro- β -carbolines (1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles) is well known (51OR151), and many examples have been described. We have therefore chosen this plethora some recent transformations of Trp that allow some general conclusions about the stereochemistry of this transformation.

Many indole alkaloids are formed *in vivo* from L-Trp and its derivatives. The Pictet–Spengler reaction of L-Trp with aldehydes follows the biosynthetic route and is therefore one of the most important synthetic methods in alkaloid chemistry (50OR151). A variety of aldehydes have been used for these purposes, from formaldehyde and acetaldehyde to other, more complex aldehydes [36JBC(113)759; 41JCS153; 48JA219; 59BSF1866;

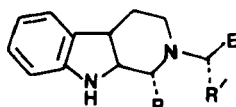
71CC908; 73CC886, 73JMC418; 74CPB2614; 79JOC535, 79TL3225; 80JHC595; 81JOC164; 83CC1147].

In all cases, mixtures of *cis* and *trans* diastereoisomers are reported. In terms of experimental observation, it is now possible to prepare 1,3-disubstituted tetrahydro- β -carbolines and 1-substituted tetrahydro- β -carbolines of known absolute stereochemistry. For example, if optically active *N*-benzyltryptophan methyl ester of known chirality reacts with aldehydes in refluxing benzene, the *trans* derivative is obtained. Arylglycidate was also used in the synthesis instead of aldehydes (78CPB2305).

When alkylated with β -(3-indolyl)ethyl bromide and subsequently treated with various aldehydes, AAs are transformed into a mixture of **121** and **122** having high to very high diastereoisomer ratios (from 72:28 to 98.5:1.5). The predominant isomer was shown to have the structure **121** from X-ray analysis. The diastereoselectivity is particularly influenced by the size of the side chain in the starting AA ester (93TL5867).



(121)

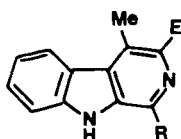


(122)

For the preparation of 3,4-dihydro- β -carbolines the Bischler–Napieralski reaction is widely used (51OR74). Since this reaction requires rather drastic conditions, *N*-acetyl tryptophan and its analogs yielded 1-methyl- β -carboline (harman) rather than 1-methyl-3,3-dihydro- β -carboline-3-carboxylic acid derivatives owing to accompanying decarboxylation and aromatization (41JCS153; 50JA2962).

For the synthesis of the natural blue pigment trichotomine dimethyl ester, L-Trp-OMe was used as a starting material. The first step of this synthesis was conversion into methyl 1-methyl-3,4-dihydro- β -carboline-3-carboxylate with acetyl chloride in TFA (85JOC3322). An improved method starts from the corresponding thioamides via thioiminium salts which cyclize spontaneously in refluxing solvent (82CPB4226). *N*-Formyltryptophan also cyclized readily with no side reactions (68CJC3404).

As an intermediate in the synthesis of lavendamycin, the fully aromatic **123** was obtained from 2-methyltryptophan and 8-methoxyquinoline-2-carboxylic acid (84TL923).

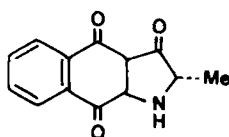


R = methoxyquinolyl-2-

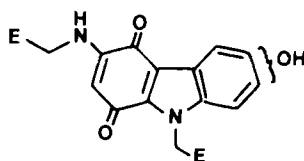
(123)

C. OTHER SYSTEMS

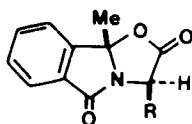
L-Alanine can add to 1,4-naphthoquinone as a nucleophile in a conjugative addition reaction; after cyclization, **124** was obtained (75MI1). Upon reexamination of the reaction of esters of AAs with quinones, it was shown that Gly-OEt with 1,4-benzoquinone gave two products: the main product was the quinone with two glycine molecules added at positions 2 and 5, and the minor product was compound **125** (71T1831). If AAs are protected with *o*-acetylbenzoic acid, **126** is formed as a by-product in 2.7–42% yield (90CC679). Esters of *N*-phthaloyl-AAs are photochemically transformed by three types of reactions. As a result of a diradical cyclization, *tert*-leucine gave **127** after abstraction of a methyl hydrogen atom (92CB2467).



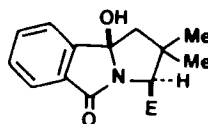
(124)



(125)

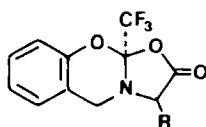


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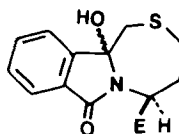


(127)

N-(2-Hydroxybenzoyl)-AA, prepared from salicylaldehyde and an AA, when reduced and cyclized with TFAA, afforded 1,3-oxazolo[2,3-*b*][1,3]benzoxazinones **128** as a new heterocyclic system [93H(36)2811]. In another group of AAs, the methyl group is transformed into a methylene group to give a benzazepinone derivative. From Met ester the *cis* and *trans* isomers of compound **129** were obtained in a 48:52 ratio (92CB2467).

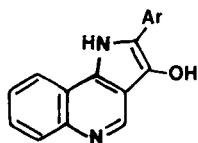


(128)

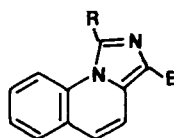


(129)

Methyl phenyl- or *p*-chlorophenylglycinate afforded with 4-chloroquinoline-3-carboxylate a pyrrolo[3,2-*c*]quinoline derivative **130** [89H(29)899]. Alkyl α -(2-quinolyl)glycinate was transformed into imidazo[1,5-*a*]quinoline **131** with DMF-DMA, TOF, or DEMA [91JHC1715, 91ZN(B)1110].



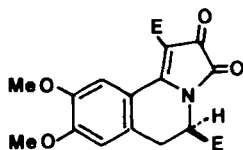
(130)



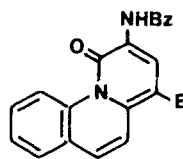
(131)

In the first total synthesis of the alkaloid erysotrine, the pyrroloisoquinoline ring **132** was prepared from (*S*)-3,4-dimethoxyphenylalanine methyl ester and methyl chloroformylacetate, followed by ring closure and condensation with oxalyl chloride [92H(33)497].

Methyl 2-benzoylamino-3-dimethylaminopropenoate afforded with methyl 2-quinolyacetate a pyrido[1,2-*a*]quinoline derivative **133** (94JHC125).



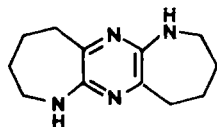
(132)



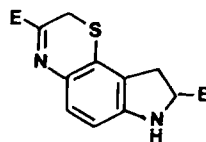
(133)

If secondary AAs are heated in the presence of aldehydes containing a proximate terminal double or triple bond and then condensed, decarboxylation and intramolecular cycloaddition tri-, tetra-, penta-, or hexacyclic cycloadducts with a condensed pyrrole ring are formed. An example is the reaction with sarcosine (Scheme 55) (88T4953).

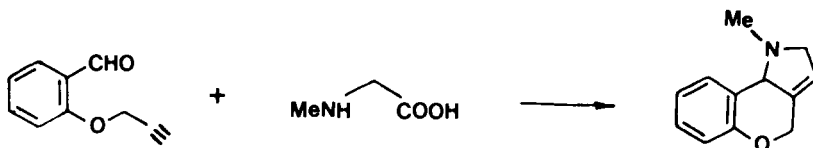
From Lys hydrochloride pyrolyzed *in vacuo* at 600°C for 8–10 min, a tricyclic compound **134** is formed in low yield (80TL2679). Cystine reacts with dopachrome to give an unstable product, but the methyl ester of dopachrome gave a stable pyrrolo[2,3-*h*][1,4]benzothiazine **135** (87T5357).



(134)

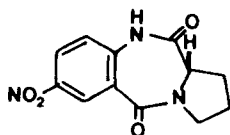


(135)



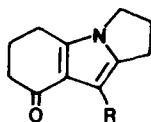
SCHEME 55

The chemistry of pyrrolo[2,1-*c*][1,4]benzodiazepines was recently summarized in a review article (94CRV433). From L-Pro or from its 4-hydroxy or other derivatives pyrrolo[2,1-*c*][1,4]benzodiazepines were prepared as key intermediates in the synthesis of anthramycin, the antibiotic tomaymycin, or their congeners. All these products possess the skeleton **136** resulting from the reaction between 5-nitroisatoic anhydride and L-Pro (68CPB480, 68JA5641; 71CPB2289; 75CC742; 78JMC1087; 82CC741; 84TL5505; 85TL4871; 89JHC1023; 91JOC2237). Condensation with isatoic anhydride was also conducted in the presence of the enzyme catalase (91JOC2237).



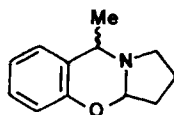
(136)

Derivatives of the related pyrrolo[1,2-*a*]indole system **137** were prepared either from *N*-acyl Pro or from the sodium salt of L-Pro and 1,3-cyclohexanediones (73JOC3487; 75JOC1260).

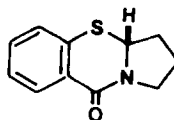


(137)

L-Proline also reacts with 2-hydroxy-6-methylacetophenones in boiling DMF to give racemic pyrrolo[2,1-*b*][1,3]benzoxazines **138** (79JOC4005). For the synthesis of pyrrolo[2,1-*c*][1,4]benzothiazepines **139**, three different syntheses from L-Pro and 2-methylthiobenzoic acid or the disulfide of *o*-mercaptobenzoyl chloride have been described (88JHC1007).



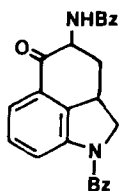
(138)



(139)

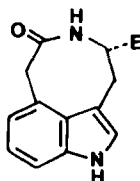
Since Trp was successfully converted into lysergic acid (84JA1813), it was further used as the precursor of various compounds having partial ergot structures (90TL7583). Thus, the first total synthesis of two ergolines, lysergine and setoclavine, was achieved (84JA1813). The same skeleton

140 was also obtained and was further transformed into rugolovasines, which are alkaloids from *Penicillium islandicum* (80JA5427). From *N*-



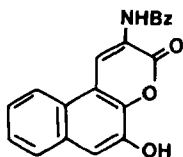
(140)

di-chloroacetyl Trp-OMe a pyrrolo-[4,3,2-*f,g*][3]benzazocine **141** was obtained in 58% yield upon irradiation (66JA3941; 88CC587).

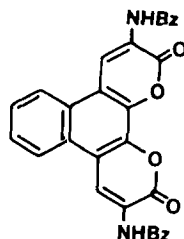


(141)

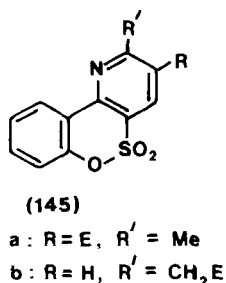
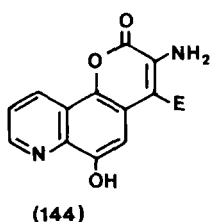
A number of tricyclic or tetracyclic systems with an α -pyrone ring were prepared from methyl 2-benzoylamino-3-dimethylaminopropenoate and hydroxy- or dihydroxynaphthalenes or 1,4-naphthoquinone (90JHC1021, 90JHC1873; 92JHC831). From 2,3-dihydroxynaphthalene the tricycle **142** and tetracycle **143** were obtained (92JHC831). With 5,8-quinolinequinone the aza analog **144** was obtained whose structure was confirmed by X-ray analysis (94H847). On the other hand, when melted with phenyl 4-chromanone-3-sulfonate methyl 3-aminocrotonate gave a mixture of two benzoxathiino[4,3-*b*]pyridines **145** in a ratio of a : b = 1 : 5. A mechanistic interpretation for this transformation is outlined in (88JHC699).



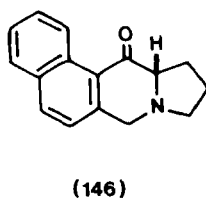
(142)



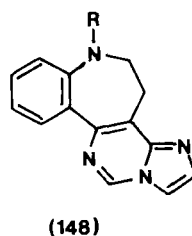
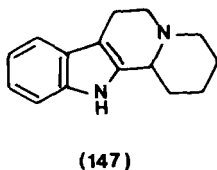
(143)



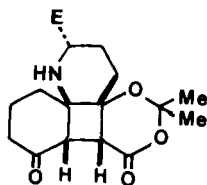
Several tetra- and pentacyclic systems were prepared from Pro, which was first *N*-substituted with naphthalene or phenanthrene rings whereupon the cyclization took place. Such reactions were used for synthetic approaches toward alkaloids vinceten from *Cynachum vincetoxicum* (the tetrahydrobenzo[*f*]pyrrolo[1,2-*b*]isoquinoline system **146**) (79LA1212; 84AJC819) or tylophorine (65T2573).



L-Tryptophan was used for the synthesis of octahydroindolo[2,3-*a*]quinolizines **147** (64CB2463; 74CPB2614; 81JOC4914), and the tetracyclic system **148** was obtained from α -AAs and 4-chloro-6,7-dihydro-5*H*-pyrimido[5,4-*d*][1]benzazepine (93JHC233).



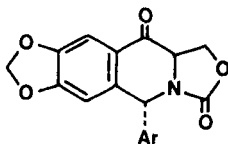
L-Glutamine methyl ester was used in the synthesis of the alkaloid histri-
onicotoxin ring system. After condensation with 1,3-cyclohexanedione and
photocyclization, the intermediate **149** was obtained (86TL5177).



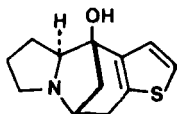
(149)

As previously mentioned, for the simpler cases, esters of secondary AAs and aryl aldehydes with an ω -alkenyl group undergo intramolecular cycloaddition to give various tetra-, penta-, and hexacyclic rings (79TL3877; 90T2213). If imines of AA esters, formed with various aldehydes, are heated in toluene to generate azomethine ylides, these undergo cycloaddition reactions with 1,4-naphthoquinones or other dienophiles to give polycyclic cycloadducts [84JCS(P1)41; 87JCS(P1)2285].

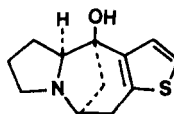
In a multistep transformation between Gly and piperonal, the tetracyclic system **150** was prepared [92H(33)537]. During the studies of *Securinenga* alkaloids, ethyl 2-thienylacetoacetate was subjected to reductive amination with L-Pro-OMe; after cyclization, two tetracyclic diastereoisomers **151** and **152** were formed (83JOC3428).



(150)

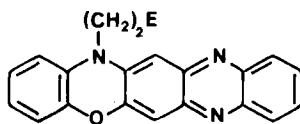


(151)



(152)

Oxidation of catechol with Ag_2O in presence of β -alanine methyl ester gave a phenoxazine-2,3-dione in low yield, and further condensation with *o*-phenylenediamine gave the pentacyclic compound **153** [78ZN(C)912].



(153)

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 23HCA411
 36JBC(113)759
 36JBC(114)341
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 37LA(529)1
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 41JCS153
 42JA1021
 43JCS39
 44BJ309
 44JA1756
 46JCS617
 46OR198
 48JA180
 48JA219
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 49JA78
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 49JA1137
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Tropones, Tropolones, and Tropylium Salts with Fused Heterocyclic Rings

Part I: Synthesis*

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I. Introduction	82
A. General Survey	82
B. Scope and Limitations	82
C. Nomenclature	83
II. Syntheses	86
A. General Syntheses of Heterocyclic Fused Tropones and Tropolones	86
1. From Other Seven-Membered-Ring Compounds with Fused Heterocyclic Rings	86
2. By Cyclizations to Form the Seven-Membered Ring	91
3. By Cyclizations to Form the Heterocycle	98
4. From Natural Sources	118
B. Syntheses of Tropones and Tropolones Fused to Individual Heterocyclic Rings	120
1. Five-Membered Rings	121
2. Six-Membered Rings	126
3. Seven-Membered Rings	129
C. General Syntheses of Heterocyclic Fused Tropylium Salts	129
1. From Other Seven-Membered-Ring Compounds with Fused Heterocyclic Rings	129
2. By Reactions Forming the Seven-Membered Ring	135
3. By Reactions Forming the Heterocycle	136
D. Syntheses of Tropylium Salts Fused to Individual Heterocyclic Rings	138
1. Five-Membered Rings	138
2. Six-Membered Rings: Benzazines	140
E. Syntheses of Tropoids Fused to Metal π -Complexes	143
1. Tricarbonyl Cyclobutadiene Iron Derivatives	144
2. Tricarbonyl Benzene Chromium Derivatives	144
References	145

*Respectfully dedicated to the Nestor of seven-membered-ring chemistry, Professor Tetsuo Nozoe.

I. Introduction

A. GENERAL SURVEY

Tropones, tropolones, and tropylium salts have been known since the early 1950s. Today, they are counted among the most important classes of nonbenzenoid aromatic compounds.

From the beginning of tropoid chemistry, many *heterocyclic* fused tropoids¹ have also been described. Some of these heterocyclic derivatives have been covered in general reviews on tropoids by Pauson (55CRV9), Šantavý (56MI2), Asao *et al.* [71MI1; 85HOU(5/2c)49, 85HOU(5/2c)710], Pietra (73CRV293), Nishiwaki and Abe [81H(15)547], Lloyd (84MI2), and, especially, by Nozoe *et al.* [56FOR(13)232; 57CCA207; 59MI1; 61MI1; 71PAC239; 73MI1; 75MI1]. Nozoe and his group have made significant contributions in this field, and Nozoe and Kikuchi wrote a special chapter on heterocyclic troponoid derivatives (60MI1).

Examples of different types of tropones and tropolones fused to a five-membered heterocyclic ring are given in Scheme 1. Different fusion with respect to the *heteroatom or group* (Z) leads to

1. hetareno[*b*]tropones (R = H) and -tropolones (R = OH) (**1a–c**) or
2. hetareno [*c*]tropones and -tropolones (**2**).

On the other hand, compounds **1a–c** are examples of different fusion with respect to the *carbonyl* group; they bear this group in the α (**1a**), γ (**1c**), and, in some cases, β (**1b**; e.g., 65BCJ306; 67MI1; 91BCJ2131 positions relative to the bridgehead).

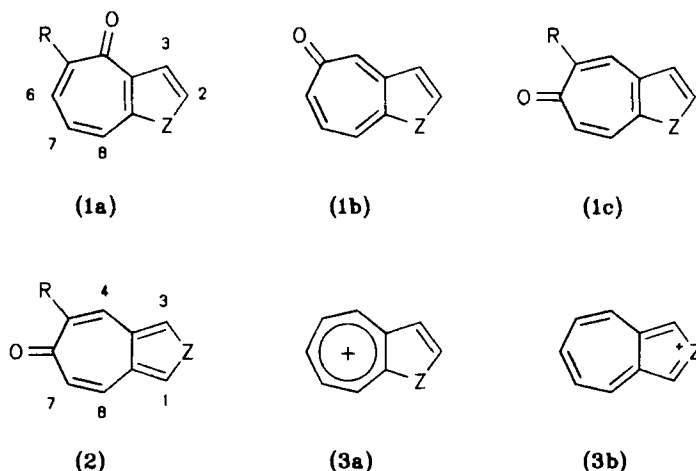
Structures **3a** and **3b** are examples of tropylium ions (see Section I,C) corresponding to tropones **1** and **2**, respectively.

B. SCOPE AND LIMITATIONS

This article reviews relevant literature from 1951 to 1993. Recent papers cited in *Chemical Abstracts* through Vol. 121 (October 1994) are covered. Patents are included if they reveal new synthetic aspects or new applications.

Coverage is restricted to tropoids directly fused to fully unsaturated heterocyclic rings or to the corresponding tautomers.

¹ According to Nozoe [56FOR(13)232], the term "tropoids" includes the three types mentioned above; "troponoids" is a common name for tropones and tropolones.



[R = H, OH; Z = O, S, NH etc.]

SCHEME 1

C. NOMENCLATURE

According to *Chemical Abstracts* (93MI1), the correct names for the compounds given in Scheme 1 (e.g., Z = O, R = H) are the following:

- 1a:** 4*H*-cyclohepta[*b*]furan-4-one (**1b** and **1c** are named similarly),
2: 6*H*-cyclohepta[*c*]furan-6-one,
3a: cyclohepta[*b*]furylium,
3b: cyclohepta[*c*]furylium.

In many papers older, less complicated names have been used, e.g.,

- 1a:** furo[3,2-*b*]tropone or 4-oxocyclohepta[*b*]furan,
3a: furo[*b*]tropylium.

Often, the exact position of tautomeric equilibria (Section III,A,4,a) is uncertain for fused troponoids substituted by hydroxy, mercapto, or amino groups. In such cases the structures preferred by the authors or the most probable tautomeric forms will be used here.

For fused tropylium ions the formulation of resonance structures is not uniform in the literature. In compounds of type **3a** a resonance structure

TABLE I
HETEROCYCLIC FUSED TROPONES PREPARED BY DEHYDROGENATION (SCHEME 2)

Fused heterocycle ^a	Position of CO ^b	Further fusion or substitution ^{ab}	Precursor ^b	Dehydrogenation agent	Reference
[<i>b</i>]furan	4	—	5,6,7,8-tetrahydro	1. PTAB; 2. Li ₂ CO ₃	73JCS(P1)968
		5,6-benzo	7,8-dihydro	S/260°C or 1. Br ₂ ; 2. -HBr (spont.)	76T829
		[5,6- <i>b</i>]naphtho	7,8-dihydro	240°C (spont.) ^c	87BSF131
		7,8-benzo[3,2- <i>a</i>]naphtho ^d	5,6-dihydro	spironaphthalenone	92T6439
	8	[6,5- <i>b</i>]thieno ^e	7,8-dihydro	1. NBS; 2. MeONa	73ACS2257
		6,7-octaleno	4,5-dihydro	DDQ	79JOC2219
[<i>b</i>]thiophene	4	[7,6- <i>b</i>]thieno ^f	4,5-dihydro	1. NBS; 2. -HBr (spont.)	73ACS2257
		—	5,6,7,8-tetrahydro	1. PTAB; 2. Li ₂ CO ₃	77JCS(P1)505
		5,6-benzo	7,8-dihydro	1. NBS; 2. Et ₃ N	66HCA214
				1. NBS; 2. MeONa	79MI1
	8	[6,5- <i>b</i>]thieno	7,8-dihydro	1. NBS; 2. MeONa	73CS(3)165
		[8,7- <i>b</i>]thieno	5,6-dihydro	SeO ₂	92IJC(B)449
		[5,6- <i>c</i>]thieno	7,8-dihydro	1. NBS; 2. MeONa	78JHC285
		2,3-benzo	4,5,6,7-tetrahydro	1. PTAB; 2. LiCl	79AP397
		[7,6- <i>b</i>]thieno	7,8-dihydro	1. NBS; 2. MeONa	73CS(3)165
		[6,7- <i>c</i>]thieno	7,8-dihydro	1. NBS; 2. MeONa	78JHC285
[<i>c</i>]thiophene	4	[5,6- <i>c</i>]thieno	7,8-dihydro	1. NBS; 2. MeONa	73CS(3)165
	6	—	4,5,7,8-tetrahydro	1. Br ₂ ; 2. LiCl/CaCO ₃	67JOC1610
[<i>b</i>]pyrrole	4	—	5,6,7,8-tetrahydro	DDQ	80JCS(P1)2081

		1-Me-7,8-benzo[3,2- <i>a</i>]naphtho	5,6-dihydro	spontaneously	64JCS5096
	8	1-Me-6,7-benzo	4,5-dihydro	1. NBS; 2. EtONa or Zn/MeOH	81EUP24807
				DDQ	84USP4440779
indole	4	—	5,6,7,8-tetrahydro	1. PTAB; 2. LiCl	76BCJ1101
	8	—	4,5,6,7-tetrahydro	S/235°C	72JOC3571
		6,7-benzo	4,5-dihydro	1. PTAB; 2. LiCl	76BCJ1101
pyrazole	4	1-alkyl/aryl-5,6-benzo	7,8-dihydro	1. NBS; 2. -HBr (spont.)	72BCJ269
oxazole	4	7,8-benzo	5,6-dihydro	1. NBS; 2. <i>t</i> -BuOK	83H(20)1581
{ <i>b</i> }pyridine	5	6,7-benzo	8,9-dihydro	DDQ	74JMC1316
	9	7,8-benzo	5,6-dihydro	$\left\{ \begin{array}{l} \text{SeO}_2/\text{pyridine;} \\ 1. \text{ NBS; 2. Et}_3\text{N (or Li}_2\text{CO}_3)^{\text{g}}; \\ 1. \text{ H}_2\text{O}_2 \text{ (or peracid); 2. Ac}_2\text{O; or} \\ \text{Pd-C/cymene} \end{array} \right\}$	$\left\{ \begin{array}{l} 64\text{BEP647043} \\ 71\text{JHC73} \end{array} \right\}$
[<i>c</i>]pyridine	5	6,7-benzo	8,9-dihydro		
	9	7,8-benzo	5,6-dihydro		
[<i>b</i>]pyridine	5	6,7-benzo	8,9-dihydro	1. NBS; 2. Et ₃ N; or S/DMF	68AF756;
					72AF133
	9	—	5,6,7,8-tetrahydro	1. PTAB; 2. Li ₂ CO ₃	73JCS(P1)968
		7,8-benzo	5,6-dihydro	SeO ₂	86JHC257
				1. NBS; 2. DBU; or DDQ	90JOC3341
[<i>c</i>]pyridine	9	7,8-benzo	5,6-dihydro	1. NBS; 2. Et ₃ N; or SeO ₂	62ZC274

^a [*b*] And [*c*] fusion as given in formulas **1** and **2**, respectively.

^b For convenience, the numbering is that of the bicyclic systems given in formulas **6a** (Scheme 2) and **13a** (Scheme 4), respectively.

^c Decarboxylation at position 3 (Cu/quinoline).

^{def} Examples of dehydrogenation products: **53a** (Scheme 13), **313**, and **314** (Scheme 78), respectively.

^g Analogous reactions led to four isomeric bicyclic cycloheptapyridinones [84JCS(P1)2297].

showing positive charge at the heteroatom (cf. 93MI1) is possible, but usually the exact degree of this contribution is unknown (Section III,B,3).

The numbering of bicyclic structures under review is that of **1a** and **2**. Different numbering of several three-membered and higher cyclic systems (93MI1) will be noted in Sections II (e.g., **53**, **118**, **159**, **237**, **258**, **276**) and III (e.g., **298**, **300**). Nevertheless, in many papers other modes of numbering were used.

II. Syntheses

A number of synthetic methods are useful for tropoids fused to *different* heterocyclic rings. These will be comprehensively treated in Sections II,A and II,C, where preference is given structurally simple examples. Sections II,B and II,D, respectively, will contain special synthetic paths to *individual* fused heterocyclic rings.

A. GENERAL SYNTHESSES OF HETEROCYCLIC FUSED TROPONES AND TROPOLONES

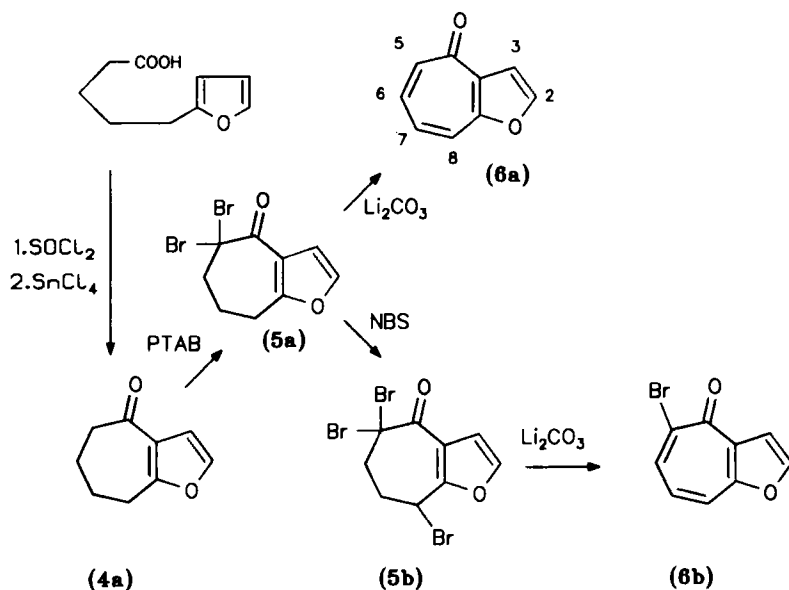
1. *From Other Seven-Membered-Ring Compounds with Fused Heterocyclic Rings*

a. *From Cycloheptenone and Cycloheptadienone Derivatives.* These ketones (type **4**, Schemes 2 and 4) are accessible by Friedel–Crafts and other cyclizations or by oxidation reactions. They require *dehydrogenation* to form tropones and, in some cases, tropolones [see 85HOU(5/2c)710]. In this way, bi-, tri-, tetra-, and pentacyclic systems have been synthesized (Table I).

The bromination–dehydrobromination route is in many cases preferable [Scheme 2; 80JCS(P1)2081], using bromine, *N*-bromosuccinimide (NBS), or phenyltrimethylammonium tribromide (PTAB). The resulting monobromo, geminal, or vicinal dibromo and tribromo derivatives (e.g., **5a,b**) are often preferentially dehydrobrominated by Jones' method [73JCS(P1)968] using lithium salts in dimethylformamide (DMF). Bases such as triethylamine, sodium methoxide, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were also used.

On hydrolysis or methanolysis, 4,5-dibromocycloheptadienones, e.g., **7** (Scheme 3), yield monobromo- and monomethoxytropones (**8,9**), respectively (76HCA866; 89CCC2443; 90HCA1197; 91GEP4037187).

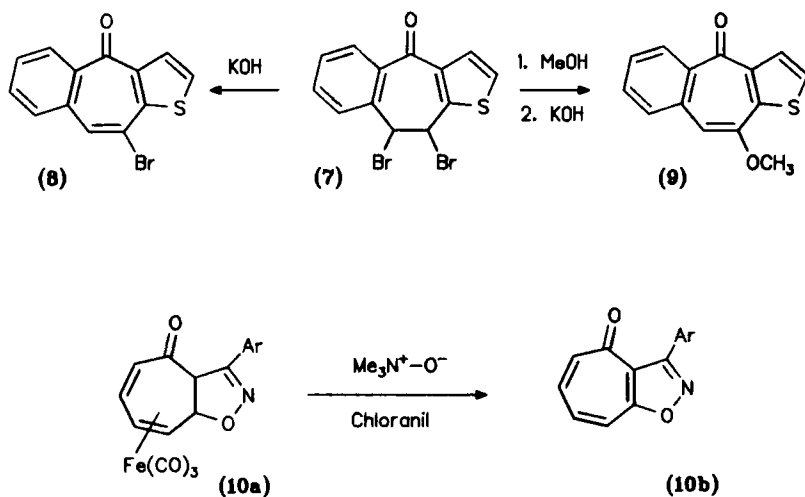
Other dehydrogenation agents include sulfur, selenium dioxide, palladium on charcoal, and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). Some reactions proceed spontaneously. Dehydrogenation also occurred



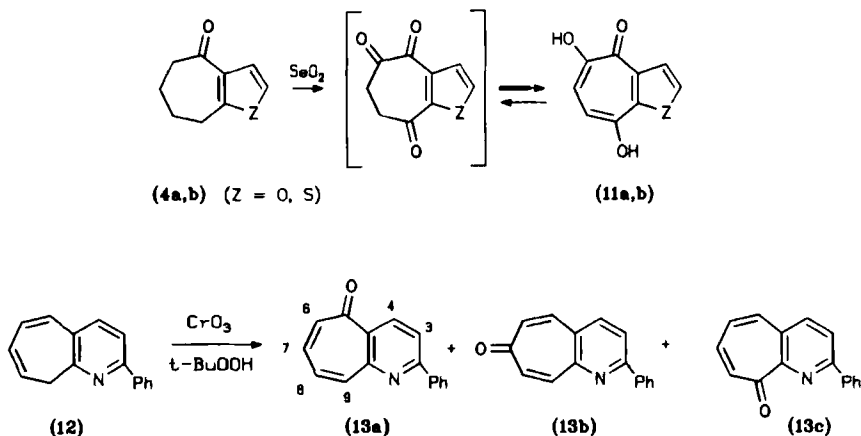
SCHEME 2

when ligands were liberated from iron tricarbonyl complexes of pyrazolo- or isoxazolo-fused dihydrotropones, e.g., **10a**, by trimethylamine oxide, occasionally in the presence of chloranil (75TL1759; 86CL1925).

Benzopyridotropones are formed on *dehydration* of the corresponding cycloheptadienolones (prepared from cycloheptenolones) by sulfuric acid (89EUP347831).



SCHEME 3



SCHEME 4

In addition to tropones, a few tropolones have been synthesized by reactions similar to those given in Scheme 2 and Table I. Hydroxyl substituents vicinal to carbonyl groups have been generated by hydrolysis of dibromo intermediates of type **5a** [78BCJ3579] and by dehydrogenation of fused cyclohepten-3,4-diones [55LA(595)203] or their monoximes [70JPR(312)466] (by Pd-charcoal or spontaneously, respectively).

Selenium dioxide causes both oxidation and dehydrogenation of fused cycloheptenones to give indolotropolone [57LA(608)38]. In the cases of furan **4a** [54CB1197] and thiophene **4b** [55LA(595)203], it effects twofold oxidation, yielding hydroxytropolones **11a** and **11b**, respectively (Scheme 4).²

b. *From Cycloheptatriene Derivatives.* Cycloheptatrienes (tropilidenes) with fused heterocycles³ have been oxidized to tropones by selenium dioxide [67CPB619], chromic acid [82IJC(B)765], hydrogen peroxide [85BCJ165; 89BCJ1158], or oxygen in air [85BCJ2840]. As a rule, only one tropone derivative (often with its carbonyl group adjacent to the heterocyclic nitrogen atom) has been isolated. Treatment of pyridine derivative **12** with chromic acid and *t*-butyl peroxide, however, afforded three isomeric tropones **13a-c**, as shown in Scheme 4 [90JCS(P1)435].

According to Nozoe *et al.*, Sunagawa *et al.*, and other authors, nucleophilic substitutions offer routes from halo-, alkoxy-, and aminocycloheptatrienes

² In the formula schemes, substituents (R) or ring atoms (Z) in parentheses refer, in the range given, to substructures **a**, **b**, **c**, etc.

³ In the case of five-membered nitrogen heterocycles, the fused systems are frequently referred to as "azaazulenes" [see 81H(15)547, 81YKG690].

to tropones, for example, to pyrrolo- (65CPB828), indolo- (72JOC3571; 75BCJ314), pyrazolo- (84JHC653), and imidazotropones (68CPB1513).

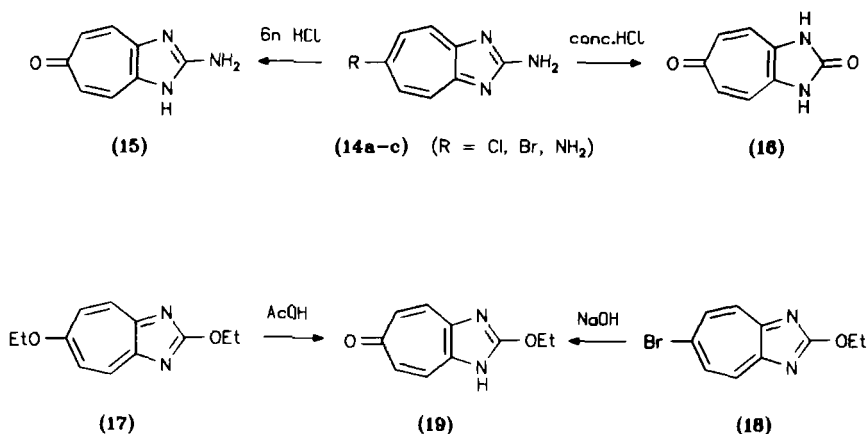
In 2,6-disubstituted 1,3-diazaazulenes, such as **14a-c** (Scheme 5; 62BCJ1188), nucleophilic substitution occurs preferentially at C-6, rather than at C-2. Attack at C-2, if possible at all, demands harsher conditions. In 2,8-dichloro-1-azaazulenes only chlorine atoms at position 8 are susceptible to hydrolysis (61YZ1799; 62YZ418; 77BCJ1184), and in 2-ethoxy-1,3-diazaazulenes **17** and **18** only the substituents at C-6 are attacked (68CPB1308). The reason is that the electron densities at the seven-membered-ring positions 6 and 8 are lower than at C-2.

Whereas 4-alkoxy-5-halocyclohepta[*b*]thiophenes resist hydrolysis (73JOC146), "benzo[*b*]tropazines" (in the nomenclature of Nozoe) such as **20** or the corresponding [1,4]thiazine (61BCJ146) behave normally. Thus, all five isomeric benzo[*b*]cyclohept[*e*][1,4]oxazinones having carbonyl groups in positions 6–10 were prepared in almost quantitative yields (91BCJ2131), e.g., 9-oxo derivative **22** (Scheme 6). Intermediate **21** was detected by reverse-phase high-performance liquid chromatography (HPLC).

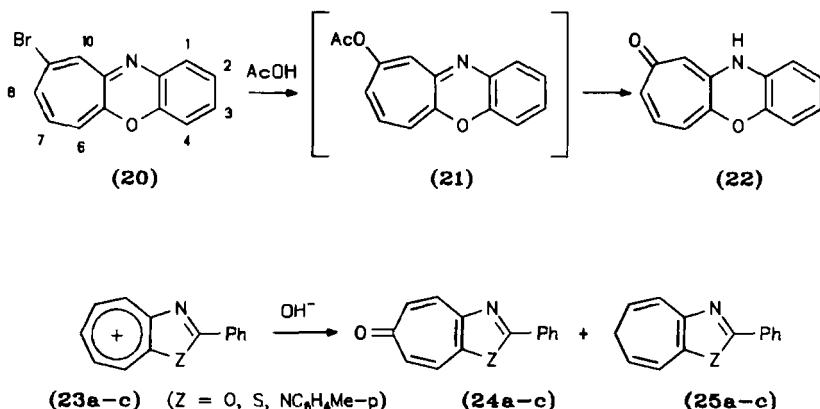
In contrast to the general reaction catalyzed by acetic acid, only 10-bromobenzo[*b*]tropoxazine was readily transformed to the corresponding tropone, even in alcohols, because position 5a is most easily attacked by nucleophiles, and a bromo atom at C-10 then acts as a good leaving group.

The product previously obtained from the 6-bromo derivative and presumed to be the corresponding tropone (79BCJ1156) was later proved to be 1-formylphenoxazine formed by ring contraction (83BCJ2756).

Hydrolysis of 6,8-dibromobenzo[*b*]tropoxazine produces 6-bromo-8-oxo and 8-bromo-6-oxo derivatives, whereas 6,8,10-tribromobenzo[*b*]tropoxa-



SCHEME 5



SCHEME 6

zine affords 6,8- and 7,9-dibromo-10-oxo isomers (the latter being a consequence of a rearrangement).

The results of selective hydrolysis together with the percentages of isomers formed suggest that the facility for hydrolytic cleavage is in the order C-10 > C-8 > C-6. This order agrees with the order of bond energies between bromine and carbon atoms as calculated by the MINDO/3 method for the five isomeric monobromobenzo[*b*]tropoxazines.

c. *From Tropylium Salts.* Treatment of tropylium salts such as **23** with aqueous alkali initiates a disproportionation leading to tropones **24** and cycloheptatrienes **25**, as shown in Scheme 6 (67CPB619; 74JMC1316). Apparently, the reaction passes through an intermediate bis(cycloheptatrienyl) ether [85HOU(5/2c)710, p. 717].

In some cases two isomeric tropones (4-oxo and 6-oxo) and two or more tropilidenes are formed from tropylium salts [66JCS(C)926] or from the equivalent pseudobases (cycloheptatrienols or tropols; 69ZOB2601). Finally nucleophilic attack can generate an unstable tropol that yields, on oxidation, the desired tropone (78AJC1607).

d. *From Tropone and Tropolone Derivatives.* On treatment with bi-functional synthons, 5-nitroso- and 5-arylazotropolones or their derivatives undergo cyclization and tautomerization to form heterocycle-fused tropoximes, e.g., **26** (Scheme 7; 58MI2, 58MI3; 61BCJ151; 74JOC2956) and arylhydrazones (56MI3; 58MI3), respectively (see Section IV,A,8,b). Tropones (e.g., **27**) are obtained from these derivatives by treatment with a mixture of formic acid and copper carbonate (Robinson's method).

By contrast, 6-iminocycloheptatriazoles (54MI1) and -imidazoles (67CPB627) can be hydrolyzed by mineral acids or bases.

Finally, tropolones (e.g., **29**; Scheme 7) were prepared by cleavage of appropriate alkoxy- or aroxytropones, such as **28** [65MI1; 71BSF1437; 72JHC967; 74BSF(2)1383; 75TL1849].

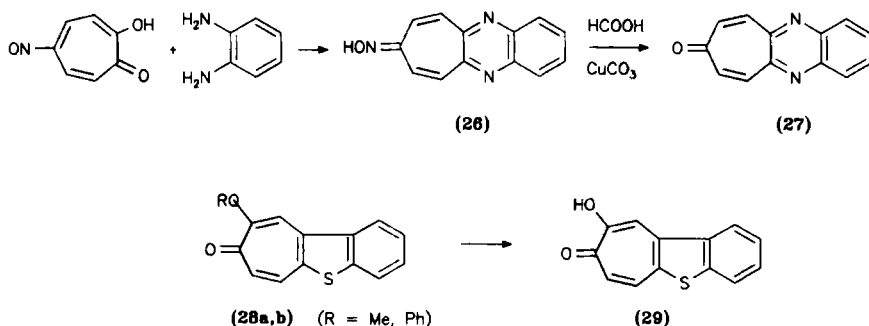
2. By Cyclizations to Form the Seven-Membered Ring

a. *By Aldol-Type Reactions.* Aldol condensations have been successfully applied to a wide variety of diformyl compounds [Table II; see 85HOU(5/2c)710, p. 718]. Examples are shown in Scheme 8 [74BSF(2)1383]. Reactions involving both unsymmetric ketones and unsymmetric dicarboxaldehydes can lead to a mixture of two isomers (e.g., **30a** and **30b**) in which substituents R and R' interchange their positions. Other reactions were reported to be regiospecific (65MI1; 70BSF3636; 72JHC967).

The condensations were catalyzed by bases, such as alkali hydroxide or alkoxide, triethylamine, and piperidine or its acetate. Some reactions (75AG840; 88AP757) proceed much more smoothly with diethyl acetone-dicarboxylate (even in the presence of diethylamine or ethyldiisopropylamine) than with, e.g., dibenzylketone (only in the presence of potassium hydroxide/morpholine or DBU). Yields vary significantly because side reactions are possible.

Unsubstituted acetone resists condensation with 2,3-diformylthiophene (71BSF1437) but, surprisingly, reacts with 3,4-diformylfuran, -thiophene, and -pyrrole or 1,2-diformylferrocene (Table II). The reactivity of hydroxyacetone allows the preparation of heterocycle-fused tropolones.

Deuterated troponoids, e.g., **32** and **33** [Scheme 9; 80BSF(1)327], result from condensations involving mono- or dideuterated diformyl compounds (D enters positions 4 and 8 in **32**) and/or perdeuterated acetone (D enters



SCHEME 7

TABLE II
HETEROCYCLIC FUSED TROPONES AND TROPOLONES FROM CARBONYL AND HETEROCYCLIC
DICARBONYL COMPOUNDS (SCHEME 8)

Fused heterocycle ^a	Substituents R/R'	Further fusion or substitution ^{ab}	Reference
[b]furan	Me, COOMe ^c	2,3-benzo	75JHC177 79PIC1889
[c]furan	(CH ₂) _n (n = 7-10) ^d	—	85MI3
	H ^c	—	68T4501
	COOMe ^c	—	91CB2465
	SMe ^c	—	83AP730
	(CH ₂) _n (n = 7-10) ^d	—	85MI3
[b]thiophene	Me, Ph, COOMe ^c	—	71BSF1437
	H/Me, OMe, OH ^e	—	—
	(CH ₂) _n (n = 5-9, 12) ^d	—	72BSF4349
	Me, Ph ^c	2,3-benzo	65MI1
	H/Me, Ph	—	—
	MeO, PhO/H	—	—
	COOEt ^c	2,3-benzo	56CB1574
[c]thiophene	—	2,3-naphtho	57CB2646
	H, Me, Ph, COOEt ^c	—	71BSF1437
	H/Me, OMe, OH	—	—
	Me ^c	—	67JOC1610
	Me/Me, Ph	—	68ZOR907
	COOEt/H, COOEt	—	69ZOR570
	SMe ^c	—	83AP730
	SOMe ^c	—	88CZ9
	(CH ₂) _n (n = 5-9, 12) ^d	—	72BSF4349
	Ph, SMe, SPh, COOMe ^c	—	88AP757
[1,3]dithiol2-thione	—	—	—
[b]pyrrole	Me, COOMe ^c	1-Me	73JHC1083
indole	COOMe ^c	1-Me	80JHC93
[c]pyrrole	H, Me, Ph, COOMe ^c	2-H	76H(4)969
	H/Me, Ph	—	—
	H, Me, COOMe ^c	2-Me	85T3303
	H/Me	—	—
[c]pyrrole	H/H, Me	2-Ph	69ZOR570
	Me/Me, Ph	2-Ph	68ZOR907
	COOMe, COOPh, COAr ^c	2-Me, Bu, Ph	90ZC437
	Me, Ph, COOMe ^c	2-H, 2-Me	75AG840
	H/SMe	2-H, 2-Me	87AP362
	SMe ^c	2-H	83AP730
	SOMe ^c	2-Me	88CZ9
	Me ^c	—	72JCS(P1)1623
pyrazole	COOEt ^c	—	72JOC676
	OMe/H	—	72JHC967
	OH/H ^f	—	—

(Continues)

TABLE II (Continued)

Fused heterocycle ^a	Substituents R/R'	Further fusion or substitution ^{ab}	Reference
imidazole	Me, Ph, Cl, COOMe ^c	1-Me	82OPP409 83JPR853 85MI2
	Me, Et, Pr, COOEt ^c	1-CH ₂ Ph	72RTC1383
	H, Me, COOEt ^c	1-biphenyl-Me	91MI1
triazole	(CH ₂) ₁₂ ^d	1-CH ₂ Ph	87MI1
	(CH ₂) ₆ -bis- ^{cg}	1-CH ₂ Ph	86JCED504
[2,1,3]thiadiazole	Cl, SMe, SEt, COOMe ^c	—	82CZ411
[b]pyridine	H/OMe ^e	—	70BSF3636
	H/OH	—	—
	Me, COOEt ^c	—	73JHC1075
	H/Me, Et ^c	—	—
[b]quinoline	COOEt ^c	—	81JCS(P1)2509
[c]pyridine	OMe, OH/H	—	70CR(C)551
quinoxaline	Me, Ph, COOMe ^c	—	{ 78PJC2045
	H/Ph	—	{ 82T3043
ferrocene	H, Me, Ph, COOEt ^c	—	69BSF1182
	H/Et, OH	—	—
benchrotrene ^h	Me, Ph ^c	—	75JOM(94)35
	H/Et	—	—

^a [b] And [c] fusion as given in the formulas **30** and **31**, respectively (Scheme 8).

^b The numbering is that used for the bicyclic system, e.g., **30**.

^c R = R'.

^d Ansa compounds.

^e Formation of two isomeric products (R ≠ R').

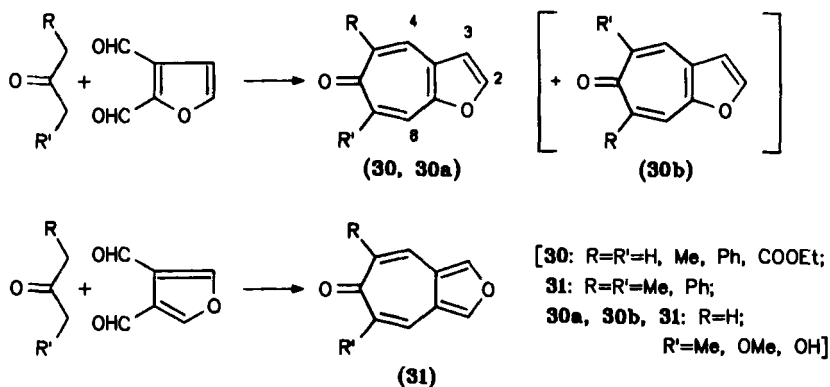
^f From bromo- or hydroxyacetone.

^g Bis-ansa compound obtained from cyclooctadecane-1,9-dione.

^h Tropone fused to benzene chromium tricarbonyl.

positions 5 and 7). Mono-, di-, and tetradeuterated heterocycle-fused tropenoids have been prepared [68T4501; 70CR(C)551; 74BSF(2)1383; 85JCS(P1)983; 86CJC1360]. Complete assignments of NMR and IR bands, distinguishing between isomeric structures, and proposals for reaction mechanisms were based on these deuterium labeling reactions.

Regiospecific two-step syntheses of distinct isomers (analogs of **30a**, **30b**) were reported by Guillard, Quéguiner *et al.* [70BSF3636; 71BSF1437; 72BSF4349; 77BSF(2)75]. Starting from partly blocked dicarboxaldehydes, such as **34**, attack at the free formyl group, cleavage of the acetal group, and intramolecular aldol reaction of **35** lead to pure tropone **36** (Scheme 9). Furthermore, diethylacetal **34** is able to condense with the less reactive

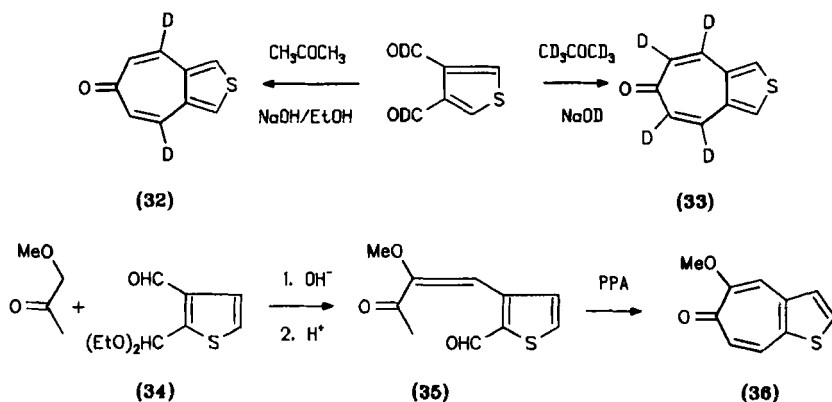


SCHEME 8

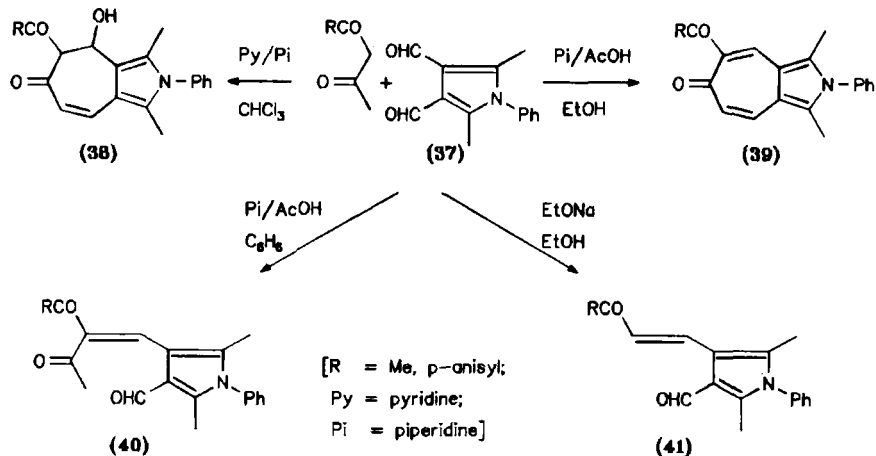
acetone; acetylformylthiophene ethyleneketals (1,3-dioxolanes) cyclize to give pure 4- and 8-methylthieno[*b*]tropones.

Even without any blocking group, but under less harsh conditions, aldol condensations proceed through isolable intermediates similar to **35** and **40** [76H(4)969]. On the other hand, during the synthesis of ansa-thieno- and ansa-triazolotropones, 4-hydroxy-4,5-dihydro derivatives (primary products of the aldol reaction, analogous to **38**) could be isolated, depending on the length of the polymethylene bridge (72BSF4349; 87JCED130).

Four different products (**38–41**) are involved in the reaction of β -diketones and pyrroledicarboxaldehyde **37** [Scheme 10; 89H(29)273]. Regarding α,β -unsaturated ketones **41**, it seems that the cleavage of β -



SCHEME 9



SCHEME 10

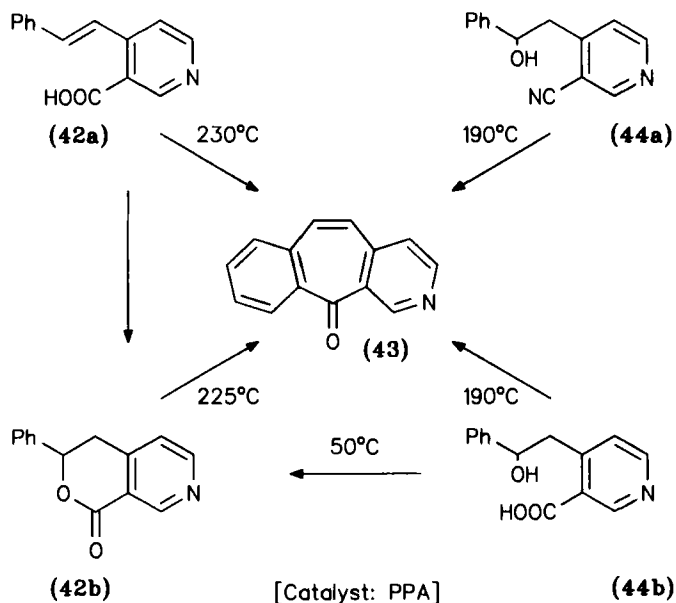
diketones under basic conditions is effected by a reverse Claisen condensation.

Finally, in imidazole-4,5-dicarboxaldehydes groups such as $-\text{CH}_2\text{OCH}_2\text{CH}_2\text{SiMe}_3$ were used to protect the heterocyclic NH group during aldol condensation (91MI1).

b. By Friedel–Crafts Reactions. Some heterocycle-fused benzotropones (e.g., **43**) have been prepared by cyclization of the appropriate styrylhetarene-carboxylic acids, e.g., **42a** (Scheme 11; 71JHC73; 72JHC1203; 85JHC555; 86JHC1331), or -nitriles (92MIP1). Usually the condensation is catalyzed by polyphosphoric acid (PPA). Both (*Z*)-isomers and (*Z*)-/(*E*)-mixtures have been cyclized in related Friedel–Crafts reactions. Tropone **43** is reported to be formed from (*E*)-acid **42a** because, under the reaction conditions used, the acid isomerizes prior to cyclization (72JHC1203; 82JHC897). This is promoted by an additional selenium catalyst.

The direct cyclization of 5-styrylpyrazole-4-carboxylic acids can be accomplished only if N-1 is substituted by methyl [83H(20)1581]. Otherwise, the three-step route (hydrogenation, cyclization, and dehydrogenation) remains an alternative (Section II,A,1,a). An exception is the cyclization of phenylbenzofuranpropionic acids which forms dibenzofurotropone systems; this reaction is accompanied by spontaneous dehydrogenation [78IJC(B)567].

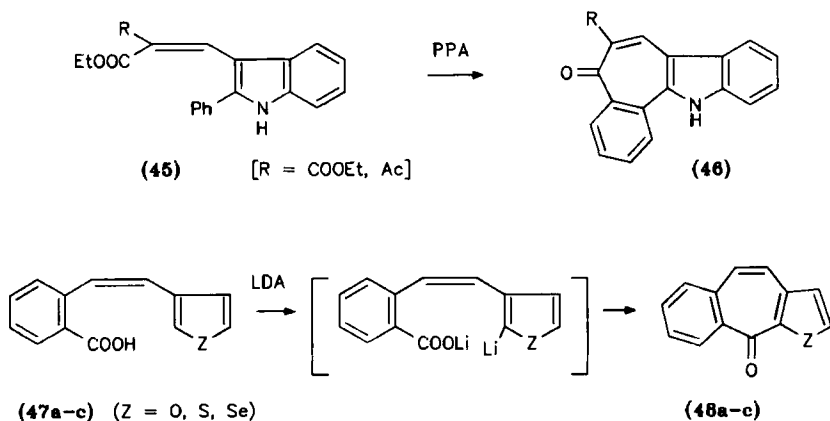
In similar syntheses, 2,2-disubstituted vinyl derivatives (e.g., **45**) were transformed to indolo- (**46**) and indolizinetropones (**300**) [Scheme 12; 84H(22)791]. Five- and six-membered-ring lactones (e.g., **42b**) and equiva-



SCHEME 11

lents **44a,b** could serve as precursors instead of the styrylcarboxylic acids mentioned above (67USP3357986; 68USP3393208; 71JHC73).

Gronowitz and co-workers prepared dithieno[*b,b'*]tropones by cyclization of pure (*Z*)-1,2-dithienylethenecarboxylic acids via acid chlorides in the presence of SnCl_4 [73CS(3)165]. The corresponding synthesis of



SCHEME 12

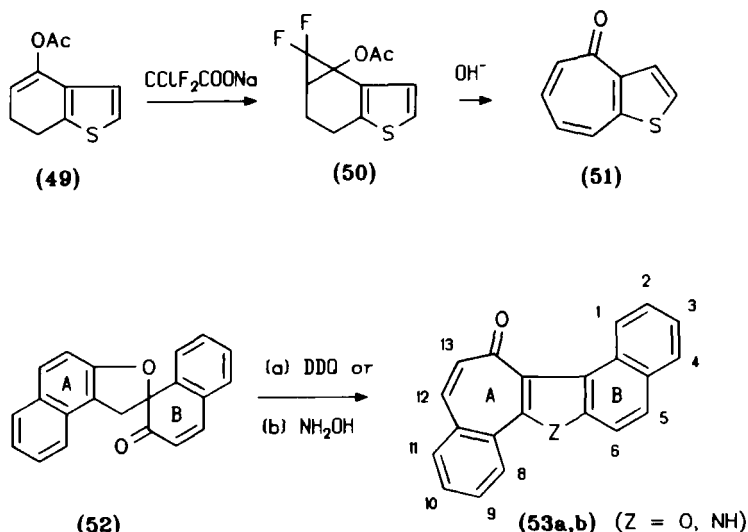
dithieno[*c,c'*]tropone and the cyclization of 2,2'-bithienylacrylic acid [92IJC(B)449] failed.

(*Z*)-3-(*o*-Carboxystyryl)thiophene **47b**, under acid catalysis, gave only a low yield of tropone **48b** (83T819). By means of lithium diisopropylamide (LDA, Parham's reaction), however, cyclization of all three isoelectronic acids **47a-c** was achieved.

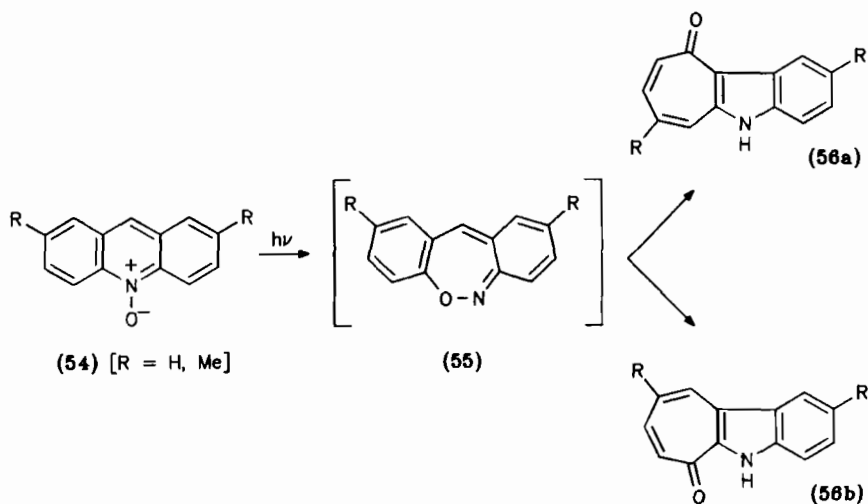
c. *By Ring Expansion.* Addition of difluorocarbene to the enol acetate (**49**) of thienocyclohexenone and hydrolysis of crystalline adduct **50** provides a convenient route to thienotropone **51** [Scheme 13; 73JA6655; see 85HOU(5/2c)710, p. 722].

Oxidation of spironaphthalenone **52** with DDQ gives furotropone derivative **53a** (92T5481), whereas reaction of **52** with hydroxylamine leads to the corresponding pyrrolotropone **53b** (64JCS5096). Quite recently it has been demonstrated that furan **53a** is not an intermediate in the formation of pyrrole **53b** and that ring A instead of ring B of **52** is converted to the tropone ring (93T113).

During photolysis of acridine *N*-oxides **54**, two isomeric indolotropones (**56a,b**) are formed, among other products (Scheme 14; 75CL401, 75CPB2818; 79T1273). As confirmed by UV spectra, the isomerization of **54** passes through intermediate **55**.



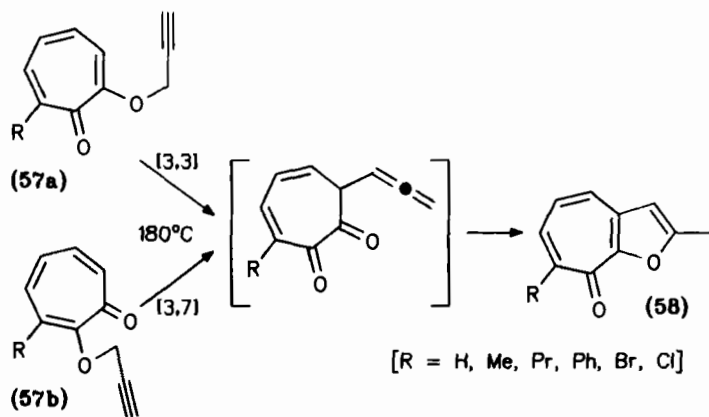
SCHEME 13



SCHEME 14

3. By Cyclizations to Form the Heterocycle

The majority of these reactions may be classified as intramolecular cyclizations, intermolecular condensations with mono- or vicinal disubstituted tropones, and cycloadditions. Detailed descriptions of heteroring syntheses have been covered in textbooks and handbooks on heterocyclic chemistry by Katritzky *et al.* [67MI2; 84CHEC(1-8); 85MI5], Palmer (67MI3), Lettau (80MI1), Gilchrist (85MI4), Eicher and Hauptmann (94MI1), and other



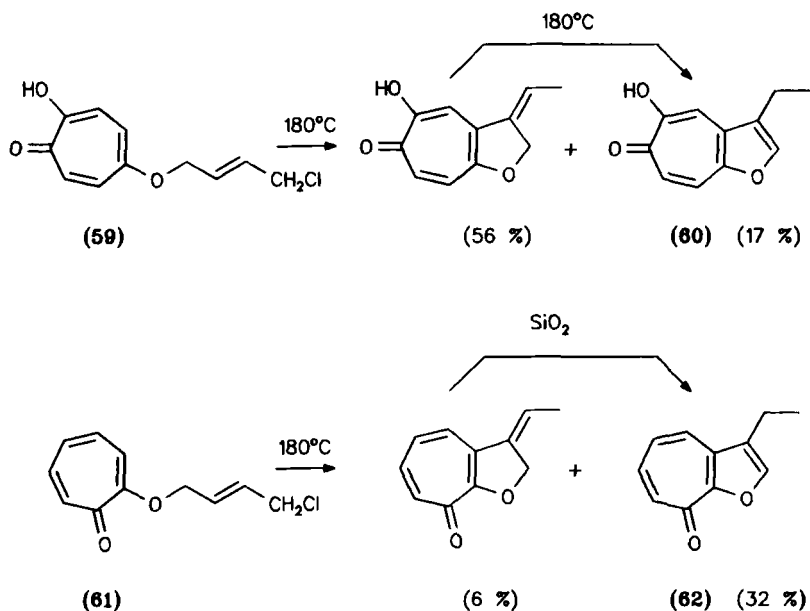
SCHEME 15

authors. Specific reactions forming individual heterocyclic systems, such as analogs of Fischer's indole or Skraup's quinoline syntheses, will be treated in Section II,B.

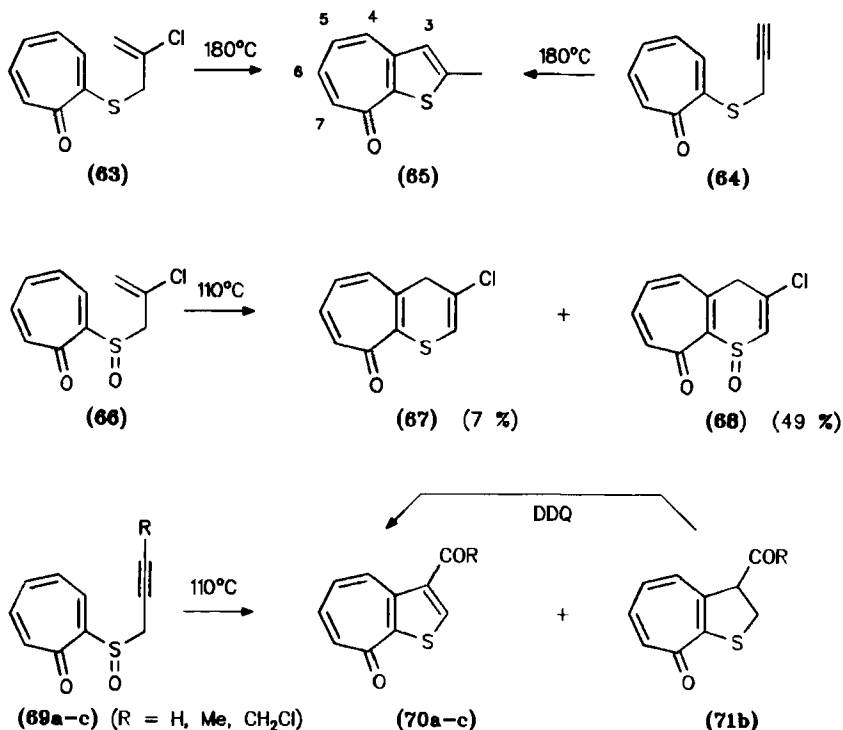
a. *By Claisen Rearrangement.* Starting from 7-substituted tropolone propargyl ethers (**57a**), Hobson and co-workers [73JCS(P1)1960; 76JCS(P1)2403], by a conventional thermal [3,3]-sigmatropic shift, generated furo[*b*]tropones **58** (Scheme 15; cf. 74HCA1598). 3-Substituted isomers (**57b**) afforded tricyclic α -diketones and tropones **58** resulting from both [3,3]- and novel [3,7]-shifts, respectively; the proportion of each depended on the nature of the substituent.

Relevant products of similar [3,3]-sigmatropic rearrangements studied by Takeshita *et al.* are shown in Schemes 16 and 17. Thus, the (*E*)-4-chloro-2-butenyl ethers of 5-hydroxytropolone and tropolone (**59**, **61**) yield furotropolone **60** and furotropone **62**, respectively [77H(6)1101; 79MI2]. By analogy, bispropargyl and bis(4-chloro-2-butenyl) ethers of 5-hydroxytropolone form difurotropones by twofold cyclizations.

In polar aprotic solvents (DMF, DMSO) above 180°C, (2-chloroallylthio)- (**63**) and propargylthiotropones (**64**) undergo *thio-Claisen rearrangements* and form thienotropone **65** in good yields [Scheme 17; 83H(20)1709].



SCHEME 16



SCHEME 17

This reaction is applicable to a dithienotropone synthesis starting from tropone 2,7-bis(thioether). An earlier attempt at rearrangement of 2-(allylthio)tropone with xylene as solvent failed (59MI2).

In contrast to thioethers **63** and **64**, the corresponding sulfoxides (e.g., **66** and **69**, respectively) cyclize in the course of an extremely mild thermolysis in DMF at 110°C [84H(22)467]. Thereby, 2-(chloroallylsulfinyl)tropone **66** is transformed to thiopyranotropone **67** and its sulfoxide **68**. Crossover deuterium labeling experiments confirm the reaction to be a radical, non-concerted, intermolecular process.

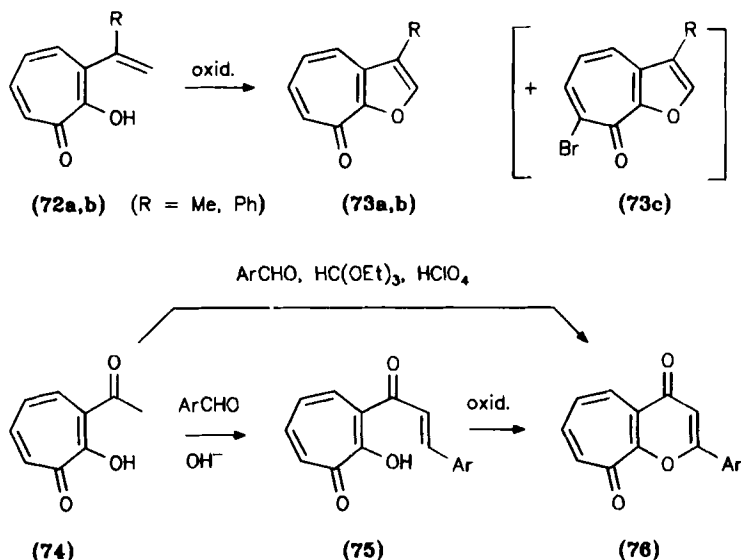
2-(Propargylsulfinyl)tropones **69a-c**, however, afford 3-acylthienotropones **70a-c**, eventually accompanied by the 2,3-dihydro derivative (**71b**), which can be dehydrogenated by DDQ [91H(32)2099]. In this case, crossover experiments demonstrate an intramolecular reaction.

It should be mentioned that 2-(allylamino)tropone in mineral acid undergoes an *amino-Claisen-like rearrangement*, but the subsequent hydrolysis of the amino group results in the formation of 2,3-dihydrofurotropone (79MI2).

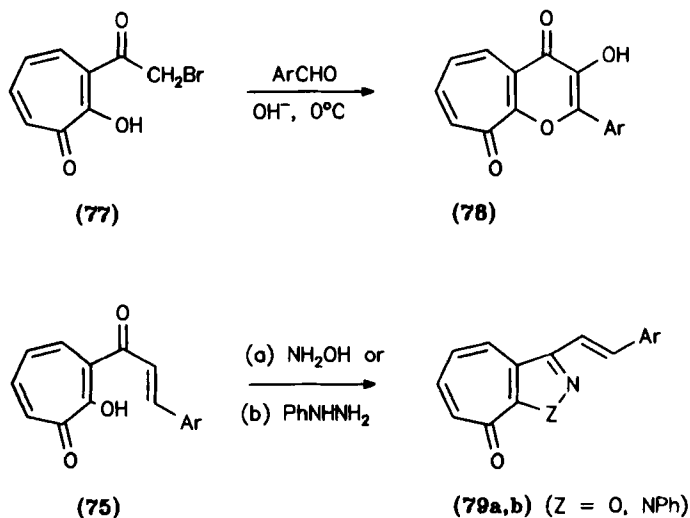
b. *By Cyclodehydrogenation.* Oxidation of 3-isopropenyltropolone (α -dolabrin, **72a**) and related substances by peracid, DDQ, bromine, NBS, or PTAB does not give the expected 3-acetyltropolone but gives instead cyclization products, furotropones **73** (Scheme 18; 80BCJ745; 82BCJ3242). Cyclization of **72a** by brominating reagents passes through an intermediate bearing the $-\text{CMe}=\text{CHBr}$ group; these reagents can cause additional bromination at C-7, forming, e.g., tropone **73c** (90JHC583; 92BCJ295).

According to Imafuku (90MI1, 90MI2), 3-cinnamoyltropolones (**75**) on oxidation cyclize in two different directions: Depending on their aryl substitution and on the reagents used (see above for **73**), they form aurone-like 2-arylidene cyclohepta[*b*]furan-3,8-diones or flavanone-like cyclohepta[*b*]pyran-4,9-diones **76** (80YGK308; 81BCJ2855). The aryl ring (Ar) may be phenyl or furyl and thienyl (85BCJ508). Cyclization by bromine requires three moles of halogen and yields the 6,8-dibromo derivative of **76** (89JHC371).

In the presence of orthoester and perchloric acid, 3-acetyltropolone (**74**) with benzaldehydes affords pyranones **76** directly (90JHC891). The reaction is considered to pass through a carbocation (from **74** and orthoester) which is stabilized by electron-donating substituents in the benzaldehyde (Ar). Therefore, the one-step synthesis might be limited to methoxy- and hydroxybenzaldehydes. These synthons are also used to prepare corresponding 3-hydroxypyranones **78** directly from 3-bromoacetyltropolone (**77**; Scheme 19; 91JHC817).



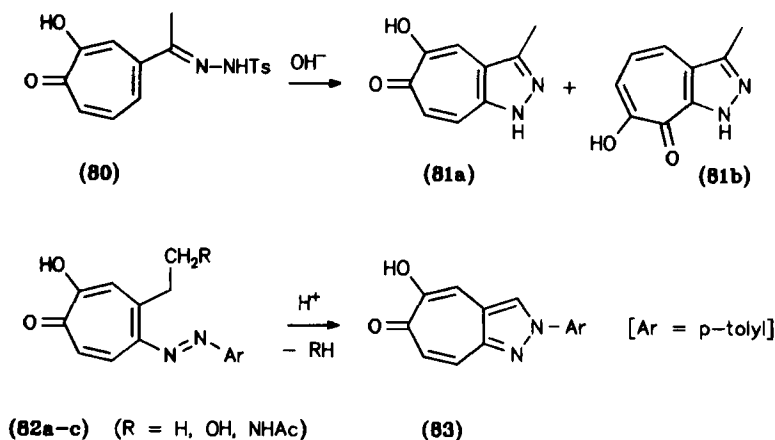
SCHEME 18



SCHEME 19

On treatment with the nucleophilic reagents hydroxylamine or phenylhydrazine, 3-cinnamoyltropolones (**75**) cyclize to form 3-styrylisoxazo- and 3-styrylpyrazolo-tropones **79a** and **79b**, respectively, without dehydrogenation (89JHC371).

Pyrazolo-tropolones **81a,b** and **83** are generated by cyclodehydrogenation of 4-acetyltropolone tosylhydrazone (**80**; 66BCJ253) and 4-ethyl-5-(*p*-tolylazo)tropolone (**82a**; 65BCJ358), respectively (Scheme 20). The dehydrogenation of **82a** is facilitated by iodine or benzoquinone. In contrast,



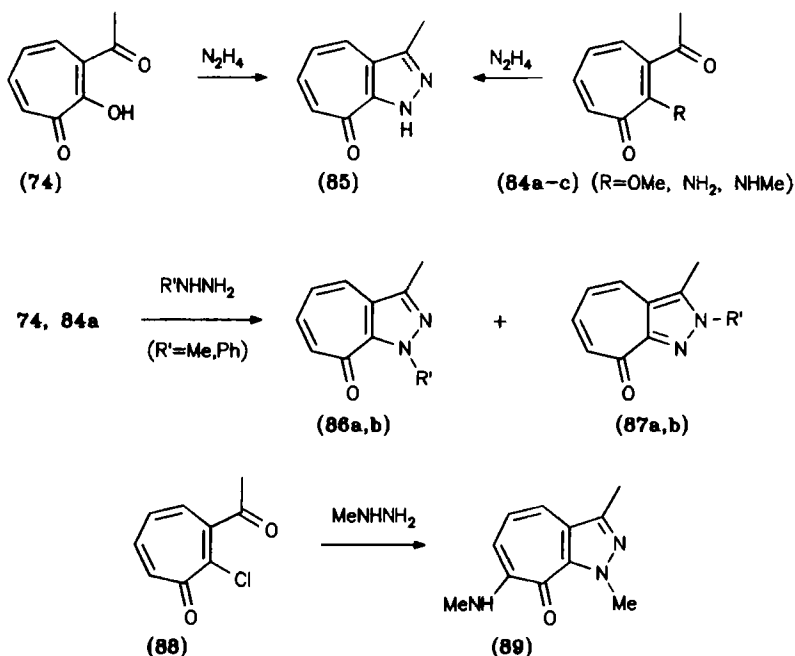
SCHEME 20

the cyclization of the functionalized ethyl derivatives **82b,c** is said to be initiated by the elimination of the OH or NHAc groups and does not involve any dehydrogenation step (65BCJ362).

c. *By Cyclization of 3-Acetyltropolone and Related Compounds.* The extensive chemistry of these substances has been summarized in less accessible reviews by Imafuku (90MI1, 90MI2) and Jin (92MI1). The reactive acetyl group and the β -diketone structure make 3-acetyltropolone (**74**) a versatile starting material for fused heterocycles, especially in condensations with nucleophiles having two reaction centers.

The reactions of **74** and its equivalents **84a-c** (bearing methoxy or amino groups in position 2) with hydrazine give pyrazolotropone **85** (Scheme 21; 79BCJ1972; 84JHC653; 92CPB1606), as does the acetyl ethylene ketal of **84a** (87BCJ185). With semicarbazide, thiosemicarbazide (81YGK862), and aminoguanidine (82JHC969), compounds **74** and **84a** react similarly. Sometimes the intermediate hydrazones can be isolated.

Consequently, the cyclizations of **74** and **84a** in the presence of alkyl- or arylhydrazines yield mixtures of two isomeric pyrazolotropones, **86a** and **87a** (80BCJ1461; 87BCJ185) or **86b** and **87b** (80JHC1293), respectively. On the other hand, condensations of 7-methoxy- (**96**) or 7-amino-2-acetyl-



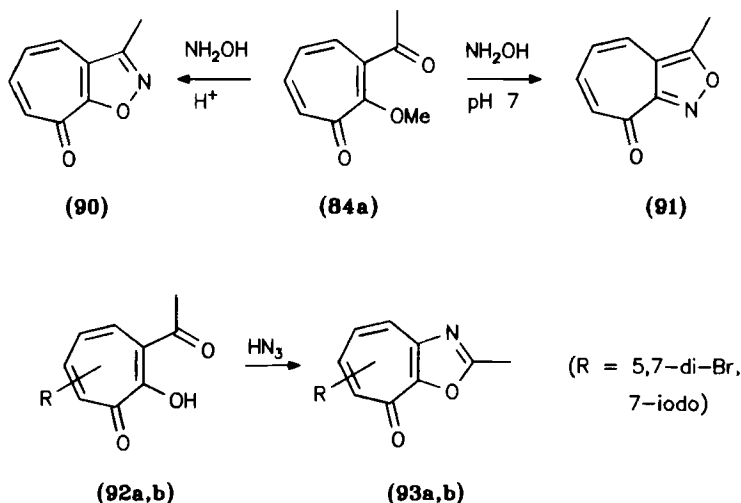
SCHEME 21

tropone with hydrazine (79BCJ1972; 84JHC653), methylhydrazine (80BCJ1461; 87BCJ185), and phenylhydrazine (80JHC1293) give pyrazolotroponehydrazones (see Section IV,A,8,b).

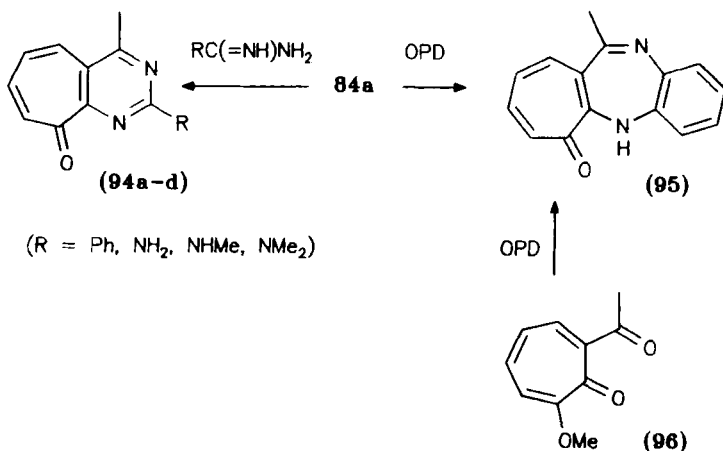
3-Acetyl-2-chlorotropone (**88**) proves to be more reactive than, for example, methoxytropone **84a** and reacts to give a rearrangement product (see Section IV,A,7,d) and unexpected tropone **89** [81H(16)935]. The latter product might be formed via hydrazone formation, cine substitution (see Section II,B,1,f), cyclization, and deamination. 3-Acetyltropolones having halogen substituents in positions 5, 6, and/or 7 cyclize with hydrazines in the expected manner (56AG247; 87JHC779).

The reactions of methyl ether **84a** with hydroxylamine give under acid or neutral conditions, predominantly, isomeric isoxazolotropones **90** and **91**, respectively, in addition to their oximes (Section IV,A,8,b) and other products (Scheme 22; 82JHC525). 3-Acetyltropolones and analogs (e.g., **88**, **96**) behave similarly (82JHC525; 87JHC779). The Schmidt reaction of halogen-substituted 3-acetyltropolones **92** affords oxazolotropones **93** (87JHC779).

Methyl ether **84a** condenses with benzamidine and guanidine derivatives to give pyrimidotropolones **94** [Scheme 23; 82JCS(P1)1037; 92JHC795], whereas isomeric methyl ether **96** yields 4-acetyl-1,3-diazaazulenes. In this reaction amidines first attack at C-7 bearing the methoxy group (of **96**), but in methyl ether **84a** the methoxy group is sterically hindered and amidines attack at the acetyl group. Finally, both methyl ethers **84a** and **96** cyclize



SCHEME 22



SCHEME 23

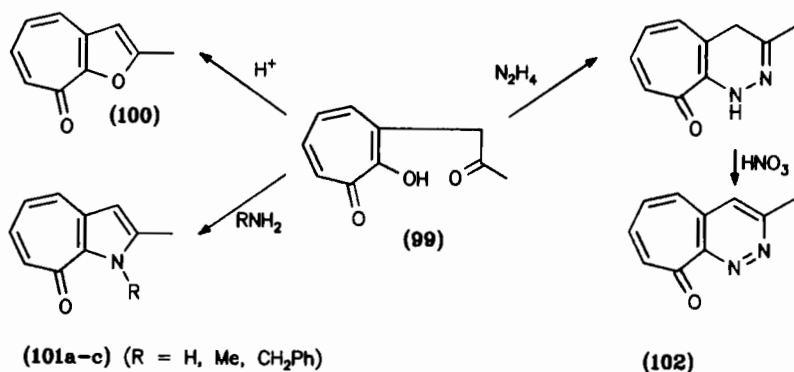
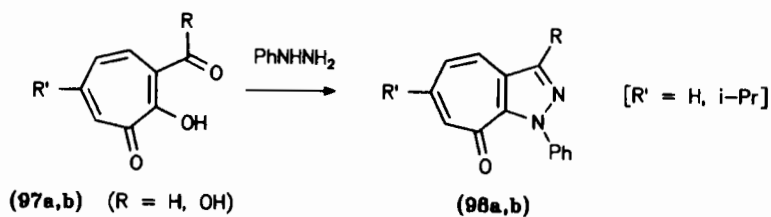
with *o*-phenylenediamine (OPD) to form, together with other products, diazepinotropone **95** (79MI3; 81JHC335).

In analogy with 3-acetyltropolone, carbonyl derivatives 3-*formyl*- and 3-*carboxy*tropolones (**97a,b**) cyclize with hydrazines to give pyrazolotropones, e.g., **98a,b** (Scheme 24; 58MI1; 91JHC717). 2-Methoxy-3-methoxycarbonyltropolone, however, with phenylhydrazine yields 2-phenylcycloheptapyrazole-3,8-dione. Phenylhydrazine attacks at the more reactive carboxyl group (in **97b**) or at the C-2 methoxy group (in the ester), respectively. 3-(Bromoacetyl)tropolone (**77**) reacts with thiophenol or heterocyclic thiols to give thioethers which cyclize with hydrazines to yield 3-thiomethylpyrazolotropones [e.g., **621**, Part 2, Scheme 168; 90H(31)677; 91JAP03/74367].

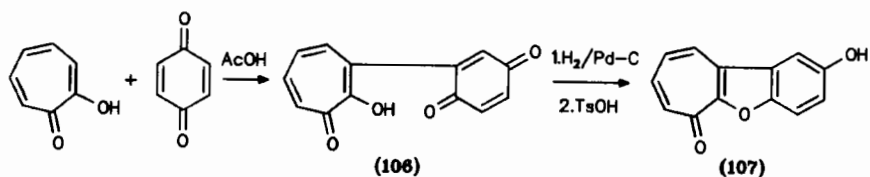
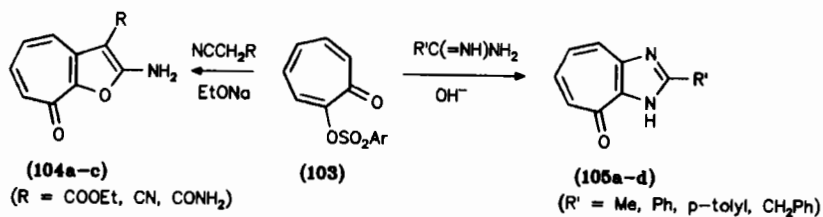
Starting from 3-acetyltropolone **99**, tropones fused to furan (**100**), pyrrole (**101**), and (after dehydrogenation) pyridazine (**102**) are accessible (65BCJ301; 68BRP1114916; 69MI1).

d. *From Bifunctional Tropolones and Their Esters.* Condensation of tropolone arenesulfonates (**103**) with CH-acidic acetonitrile derivatives is initiated by the nucleophilic attack of the anion at the reactive site C-7, as established by deuterium labeling (65TL3659). Under strongly basic conditions, the proposed reaction course involves elimination of arenesulfinate and cyclization to give 2-aminofurotropones **104a-c** (Scheme 25; 71T6023). In the reaction of tropone **103** with amidines, synthesis of imidazotropones **105a-d** was realized (69MI1; 70JAP70/31171).

Reaction of tropolone with *p*-benzoquinone and spontaneous dehydrogenation yield 3-(*p*-benzoquinonyl)tropolone (**106**), which is hydrogenated and cyclized to give benzofurotropone **107** (62BCJ349, 62MI1).



SCHEME 24

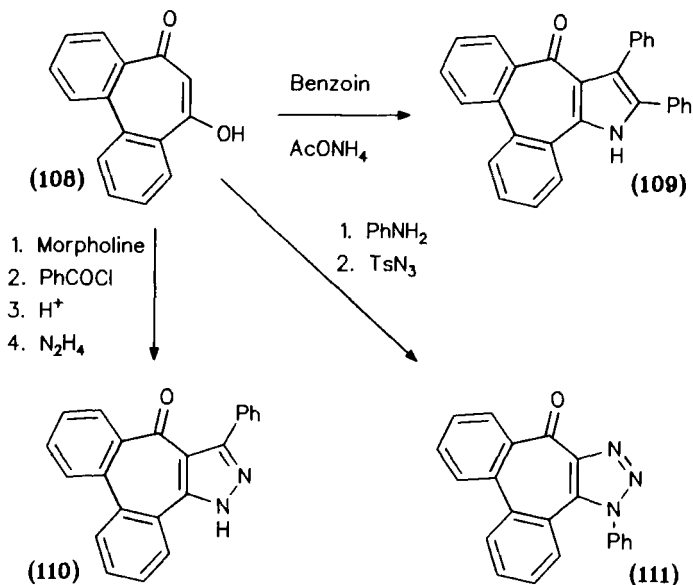


SCHEME 25

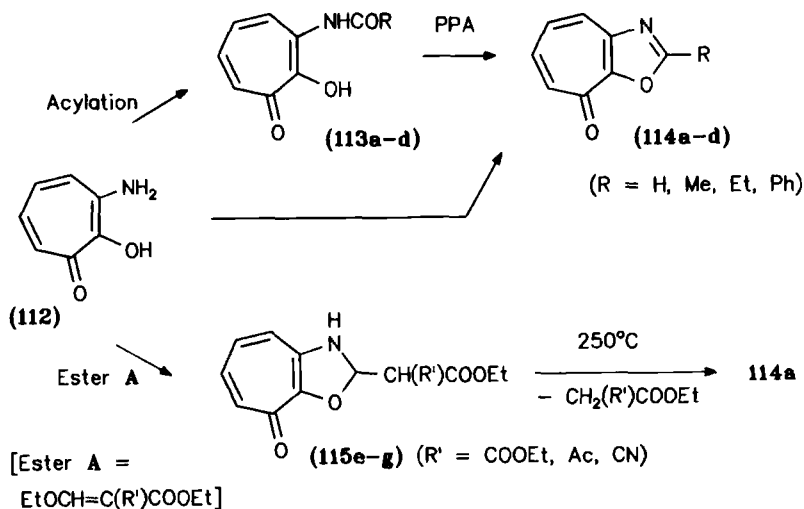
The syntheses shown in Scheme 26 (71CB1573) are based on dibenzo- β -tropolone (**108**) and its enamines. Condensation of **108** and benzoin in the presence of ammonia affords pyrrole **109**. The morpholino enamine gives pyrazole **110** via benzoylation, hydrolytic elimination of morpholine, and cyclization, whereas diazo-group transfer onto the anilino enamine leads to triazole **111**. Dione **108** and *p*-nitrophenylazide in one step give predominantly the *p*-nitro derivative of **111** (92G249).

e. *From 3- or 7-Substituted Tropolones and Their Methyl Ethers.* Oxazolo[5,4-*b*]tropones (**114**; Scheme 27) and benzo-fused analogs (52JA4935) are synthesized from 3-aminotropolones (**112**) and carboxylic acid anhydrides (56MI1; 59MI3), chlorides (84JHC1055), and orthoesters (84BCJ609; 88JHC285), occasionally in two steps via 3-(acylamino)tropolones **113** (84JHC1055; 88JHC285). In the case of *p*-nitrobenzaldehyde, the cyclization presumably passes through the corresponding oxazoline which is spontaneously dehydrogenated (61BCJ312).

Unsubstituted species **114a** is prepared from tropone **112** by cyclization with formamide (61BCJ312) or with ethoxymethylene acetates and pyrolysis of intermediate oxazolines **115e-g** (60NKZ509; 61BCJ611). 2-Phenyl derivative **114d** is obtained from 2-methoxy-7-(benzoylamino)tropone with



SCHEME 26

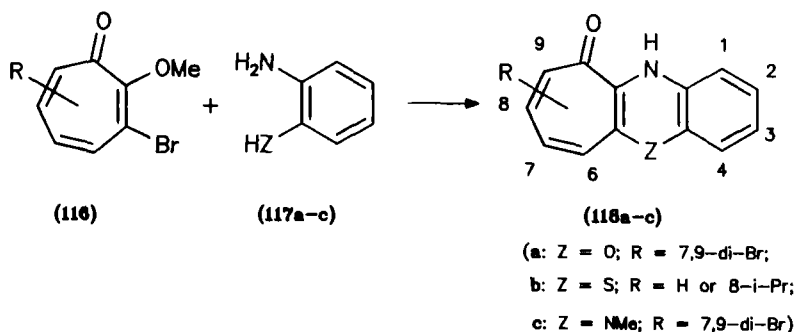


SCHEME 27

dimethyl sulfate (67CPB619). (Thiazolo[5,4-*b*]tropones prepared from **112** will be treated in Section II,B,1.f.)

Benzazinetropones **118a-c** (Scheme 28) are synthesized by the reactions of certain 2-methoxy-3-bromotropones (**116**) with *o*-aminophenol (**117a**; 91BCJ2131), *o*-aminothiophenol (**117b**; 61BCJ146), and *N*-methyl-*o*-phenylenediamine [**117c**; 89H(29)1459], respectively.

In contrast to troponone **116** (**R** = 5,7-dibromo) which smoothly yields 90% of oxazin-10-one **118a**, analog **116** (**R** = H) gives only 17% of oxazin-10-one **118a** (**R** = H) in addition to small amounts of the 6-oxo isomer (**267**) and about ten other products (83BCJ2756). The mechanisms proposed



SCHEME 28

involve cine (Section II,B,1,f) and normal substitution, respectively, of the 3-bromine atom of **116** by the amino group of **117a** to give, finally, oxazin-10-one and -6-one.

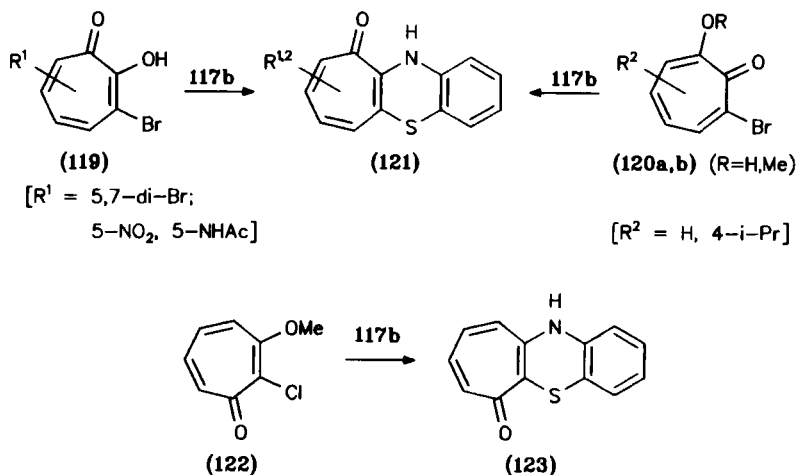
Benzthiazinotropones **121** (Scheme 29) are also prepared from 3-bromotropolones (**119**; 66BCJ1980) and from 7-bromotropolones or their methyl ethers (**120a,b**; 61BCJ146).

f. *From Other 2,3-Disubstituted Tropones.* Benzthiazinotropone **123** (isomeric with **121**) is obtained from another trifunctional tropone, **122**, as shown in Scheme 29 (66BCJ1980).

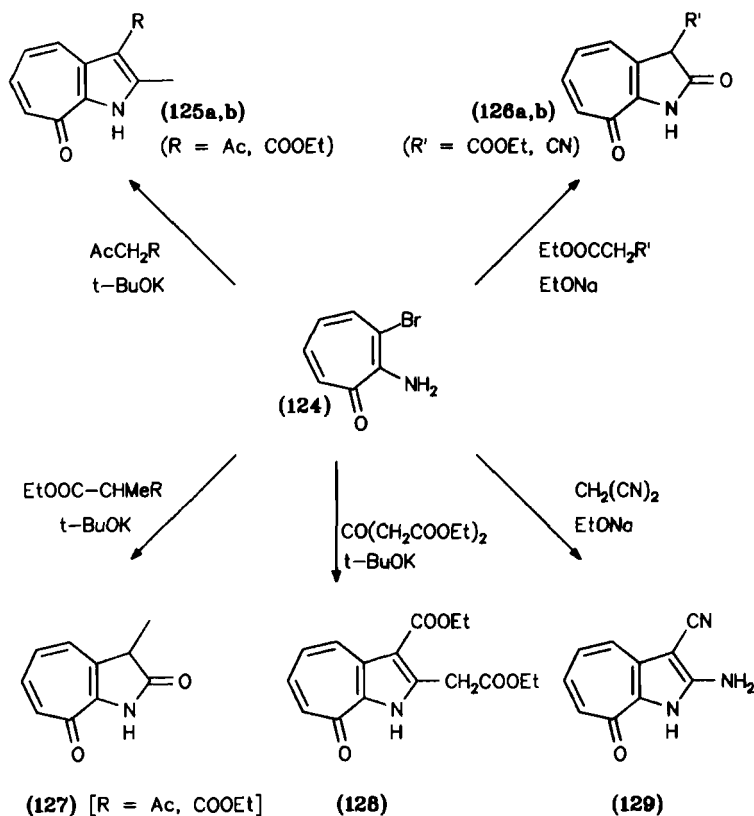
2-Amino-3-bromotropone (**124**) undergoes condensations with active methylene compounds through its bromo and amino groups to give pyrrolotropones **125–129** (Scheme 30; 62YZ418, 62YZ898; 63MI2; 65CPB473). In reactions with keto- or cyanocarboxylic esters, the amino group in **124** condenses preferentially with a ketonic rather than an ester group, and with the latter rather than a nitrile function. During the formation of pyrrolotropone **127**, the acetyl group or one of the ethoxycarbonyl groups, respectively, is eliminated.

Reactions of tropone **124** with phenylacetonitrile (62YZ892) and transformations of type **124** derivatives by several active methylene compounds (63MI2) result in rearrangements to form 8-quinolinol derivatives. (Thiazolo[4,5-*b*]tropones prepared from **124** will be treated in Section II,B,1,f.)

Finally, 2-amino-3-hydroxytropolones (**130**) are cyclized by carboxylic anhydrides to give oxazolo[4,5-*b*]tropones (e.g., **131**; Scheme 31; 55JCS1841; 70BCJ1778).



SCHEME 29

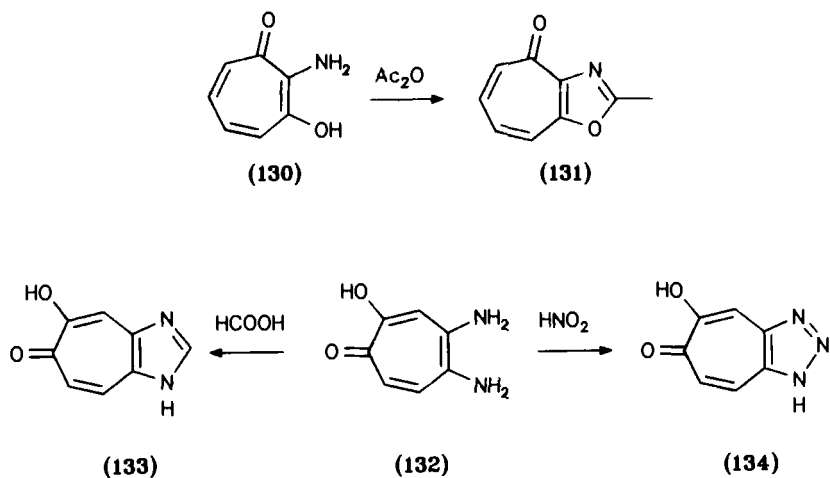


SCHEME 30

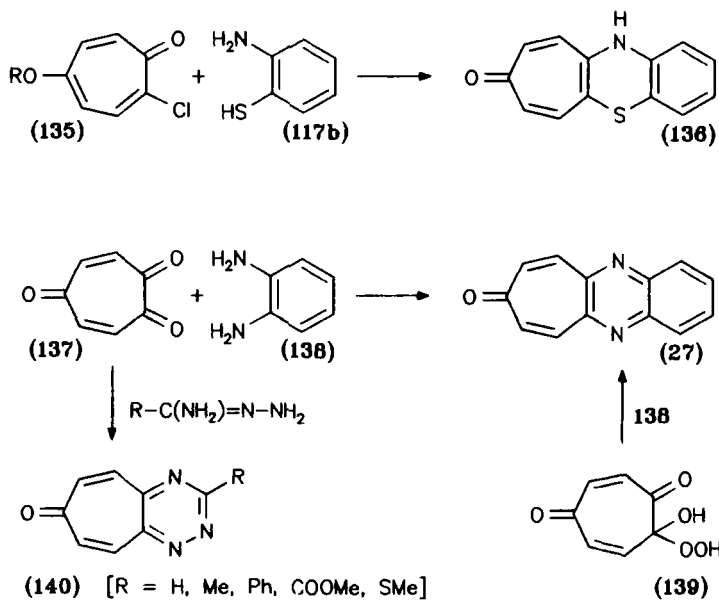
g. From 4,5-Disubstituted Tropones or Equivalents and from p-Tropoquinones. 4,5-Diaminotropolone (**132**) gives imidazole **133** on being heated with formic acid, and triazole **134** on being diazotized, as shown in Scheme 31 (61BCJ1410; 63UP1). Similarly, cyclization of 4-hydroxy-5-aminotropolone affords an oxazole derivative [61DOK(141)1380].

The condensation of 2-chloro-5-methoxytropone (**135**) with **117b** (Scheme 32) gives benzthiazinotropone **136** (66BCJ1980); the methoxy group is hydrolyzed during the fusion. In a similar reaction 2-benzoylamino-5-bromotropone with dimethyl sulfate gives oxazolotropone **24** (67CPB619).

Reactions of p-tropoquinone (**137**) are in accord with its o-quinonoid character, as shown by examples affording quinoxalotropone **27** (76TL2339) and 1,2,4-triazinotropones **140** (83LA1845). The quinone can be replaced



SCHEME 31

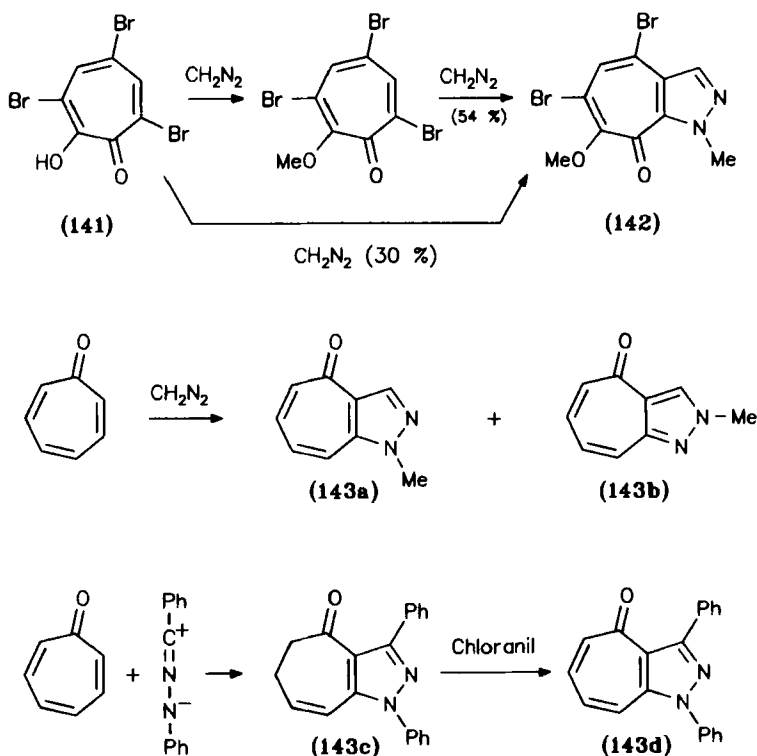


SCHEME 32

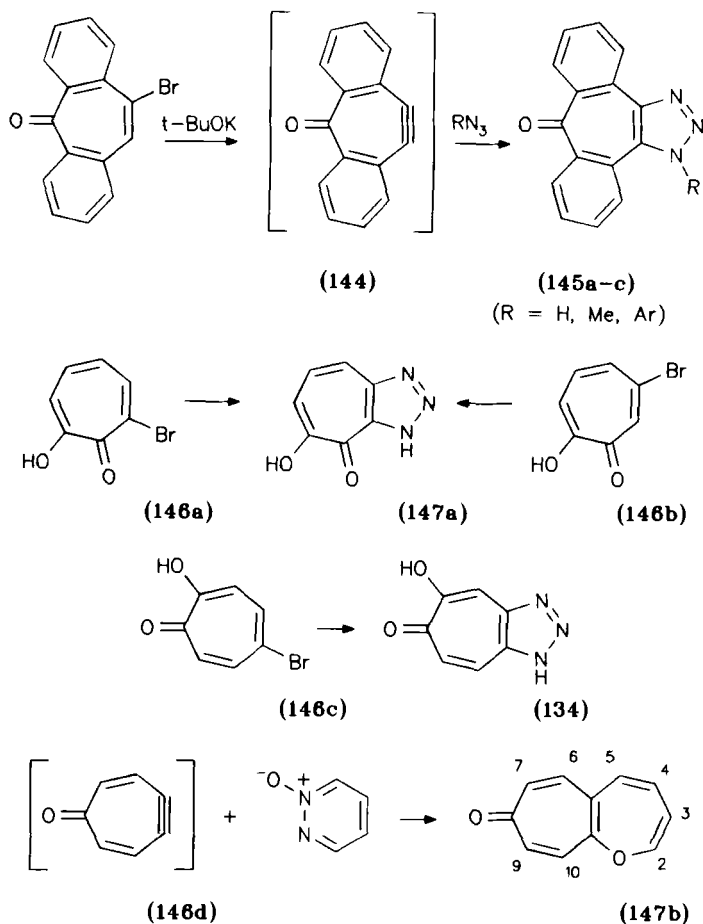
by hydroperoxide **139** (75TL1075). Fused derivatives of **137** or **138** yield tetra-, penta-, and hexacyclic quinoxalotropones [59BSF655; 67LA(705)169; 74BCJ1951; 89CL1719]. Benzo-*o*-tropoquinone hydrate condenses in an analogous manner (79CL859).

h. *By Cycloaddition.* Upon treatment with diazomethane, halogen-substituted tropolones (e.g., **141**; Scheme 33; 66BCJ253) or γ -tropolones (66BCJ1310) afford methoxy-1-methylcycloheptapyrazol-8-ones (e.g., **142**). The reactions involve a sequence of steps: *O*-methylation, 1,3-dipolar cycloaddition, dehydrogenation (or dehydrohalogenation), and *N*-methylation (71PAC239, p. 252).

Tropone itself gives with diazomethane a 3:1 mixture of 1- and 2-methylcycloheptapyrazol-4-ones (**143a,b**), along with cyclooctatrienone and 2,3-homotropone (72TL1925). Here the regiochemistry of cycloaddition is the reverse of that of diazomethane with simple α,β -unsaturated carbonyl compounds (80MI1, p.282). The different behavior of tropone and, e.g.,



SCHEME 33



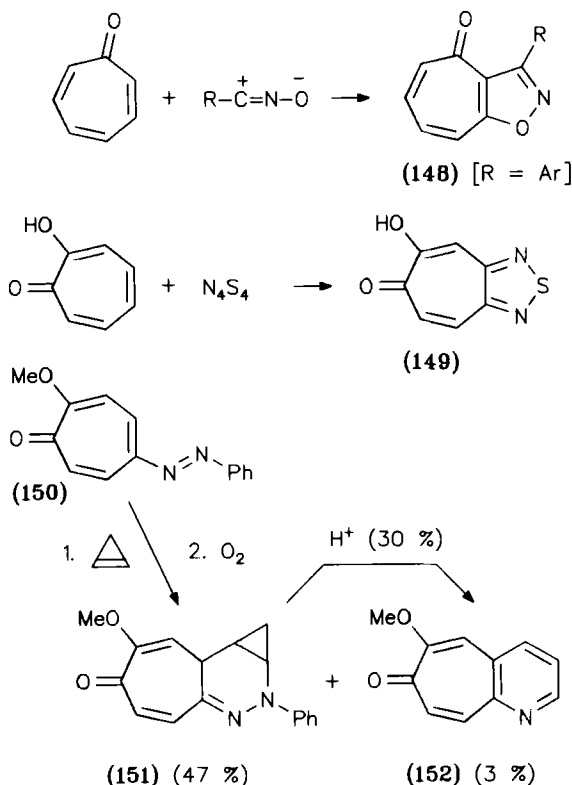
SCHEME 34

141, indicates that β -halogen substitution can reverse the orientation of cycloaddition.

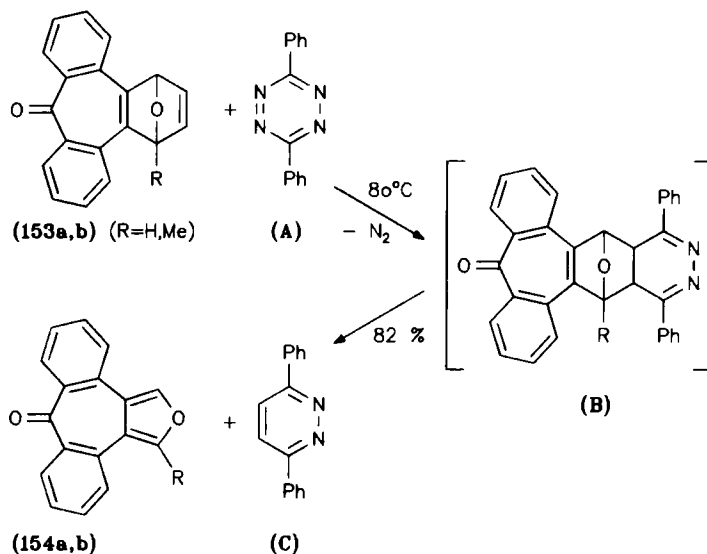
The cycloaddition of diphenylnitrilimine to tropone gives a complex mixture of up to eight pyrazolotropones and corresponding dihydro derivatives [77JCS(P1)939; 78JOC817]. Predominant product **143c** (yield 37 or 54%, respectively) is dehydrogenated to tropone **143d**. The reaction of the imine with the tropone tricarbonyliron complex, which is more reactive than tropone itself, gives a mixture of two regioisomeric complexes. This mixture is converted by cerium(IV) to tropone **143d** with little of its regioisomer [77JCS(P1)939].

In analogy with **143d**, the 2-phenyl compound is obtained from tropone and 3-phenylsydnone in a low yield [93JCS(P1)1617]. The cycloaddition proceeds *peri*- and regioselectively in a $[4\pi + 2\pi]$ mode followed by extrusion of carbon dioxide from the primary adduct and spontaneous dehydrogenation.

Dehydrotropones [**144**; 64CB1318; 67LA(705)169] and dehydrotropones (obtained from **146a-c**; 70TL1725) are described as benzyne-type intermediates in the reactions of halotropenoids with alkoxides. They are trapped by azides to give triazolotropenoids **145** and **147a/134**, respectively (Scheme 34). A kinetic study shows that the reactivity of the precursors is in the order **146b** > **146a** > **146c**. The reaction of the parent dehydrotropone (**146d**, obtained from 1-aminotriazolotropone; see Section IV,A,7,b) with pyridazine *N*-oxide results in the formation of oxepinotropone **147b** [94H(38)957].



SCHEME 35



SCHEME 36

Further cycloadditions (Scheme 35) afford, among other products, isoxazolotropones **148** (74T3765; 77G577; see Section II,A,1,a), mono- (**149**) or bis[1,2,5]thiadiazolotroponoids (89BCJ2421), and (from phenylazotropone **150** passing through intermediate diazanorcarene **151**) pyridotropolone ether **152** (77TL2663).

i. *By Thermal or Photochemical Transformation of Cycloadducts.* The reaction of 1,4-epoxytribenzotropone (oxanorbornadiene) **153a** with 3,6-diphenyltetrazine (DPT) affords dibenzofuro[4,5-*c*]tropone **154a** (Scheme 36; 76JOC1425). Presumably, the synthesis proceeds via an initially formed [2 + 4] adduct, loss of nitrogen, and *retro*-diene cleavage. Intermediates could not be obtained owing to their extreme thermal lability.

In contrast, some of the similar additions (Table III) yield isolable type-B [2 + 4]-adducts. The reaction with DPT, however, proceeds at lower temperature (80°C) than that with the cyclopentadienone derivatives (120°C) and in a high yield.

Furthermore, oxepintropones (e.g., **156a**) and azepintropones (**156b**) are synthesized by photoirradiation of oxa- and azanorbornadienes fused to tropones (**155a,b**), respectively (Scheme 37; 88CL1647; 90CL91; 92TL6487).

j. *By Transformations of Heterocyclic Rings.* Furotropone **100** is transformed into pyrrolotropone **157** by heating with amines (80BCJ3373). Un-

TABLE III
DIBENZOFURO[4,5-c]TROPONES **154** FROM CYCLOADDUCTS OF EPOXYTRIBENZOTROPONES **153**

Precursors		Yields (%)		Ene C eliminated	Reference
Ene	Diene A''	Adduct B	154		
153a	tetracyclone	^b	79	tetraphenylbenzene ^c	68CB3122
b	tetracyclone	^b	53	tetraphenylbenzene ^c	76JOC1425
a	tetracyclone	83	70	tetraphenylbenzene ^c	
a	A'	68	50	2,3-diphenyl- <i>p</i> -xylene	
a	A''	90	59 ^d	tetrachlorobenzene	
a	phenylazide	^b	77	<i>N</i> -phenyltriazole	
a	EtOOCN ₃	^b	47	<i>N</i> -ethoxycarbonyltriazole	

^a **A'** = 2,5-dimethyl-3,4-diphenylcyclopentadienone.

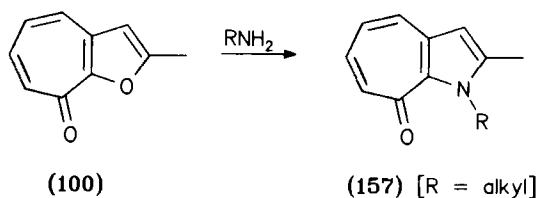
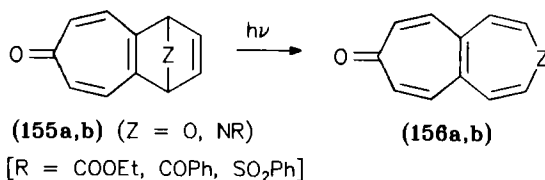
A'' = tetrachlorocyclopentadienone dimethylketal.

^b Not isolated.

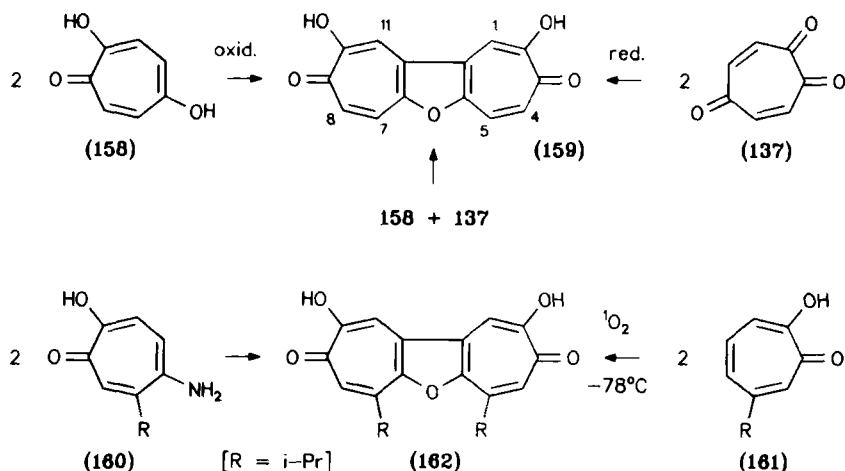
^c Elimination of CO.

^d After ketal hydrolysis.

der comparable conditions oxazolo- (e.g., **114b**) or thiazolotropones yield imidazotropones (69MI1; 91EUP432737). (Relevant examples related to furoditropone will follow in Section II,A,3,k.) Moreover, the heterocycle-exchange reaction is an important feature of tropobenzazine chemistry (Section II,D,2).



SCHEME 37



SCHEME 38

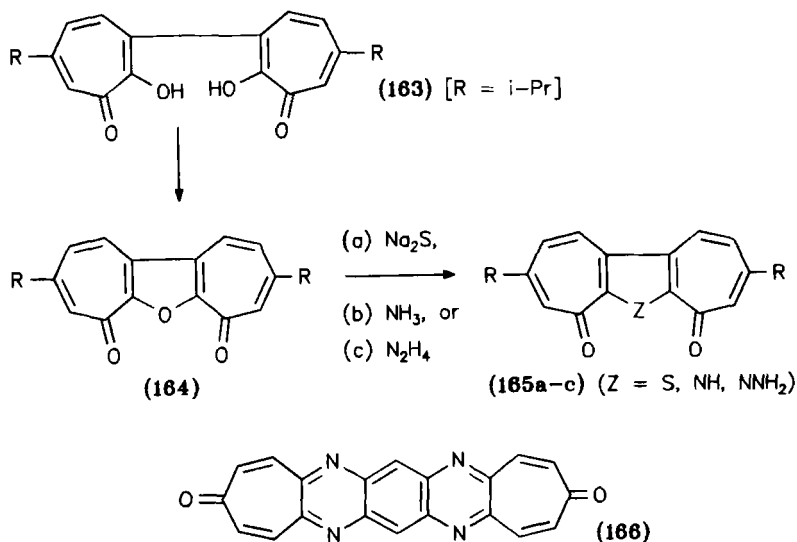
k. *By Cyclization to Form Heterocyclic Ditroponoides.* Furoditropolone **159** (Scheme 38) can be obtained by oxidative dimerization of 5-hydroxytropolone ("tropohydroquinone") **158**, by reductive dimerization of *p*-tropoquinone **137**, and by coupling (comproportionation) of hydroquinone **158** and quinone **137**. The C—C bond formation occurring at the 4,4'-positions was elucidated by deuterium-labeled reactants (82CL701).

Partial oxidation of **158** by bromine yields bromine-free **159** together with mono-, di-, and tribromo derivatives. Other useful reagents are nitrous acid (54JCS286) or the one-electron oxidants silver acetate (in substoichiometric quantity) and cerium(IV) ammonium nitrate (only for the methyl ether of **158**; 86BCJ511).

Surprisingly, the partial reduction of quinone **137** is best achieved by refluxing in acetic or propionic acids (yield 67%). Thereby the acids suffer oxidative decarboxylation (82CL701; 85BCJ515). Two further unexpected routes are based on the redox reaction with cycloheptatriene (85BCJ2072) and electrolysis under the conditions of the cyclic voltammetry measurements (87BCJ2497), respectively.

Deuterium labeling reveals that during coupling (e.g., of **158** and **137**) a rapid redox equilibrium must occur in this system (82CL701). Also the mixed condensation of unequally substituted reactants was investigated (85BCJ515).

The natural product utahin (**162**), characterized as the 5,7-diisopropyl derivative of **159**, presumably has been synthesized for the first time by oxidation (sodium bichromate) or diazotation of 5-aminohinokitiol (**160**;



SCHEME 39

51MI1; 55CRV9, p.99). It was later prepared by coupling of 4-isopropyl-*p*-tropoquinone with 5-hydroxyhinokitiol or by a biomimetic photooxidation of hinokitiol (**161**) sensitized by tetraphenylporphin (83CL1371). These reactions exemplify the "phenol oxidation" in troponoid chemistry.

3,3'-*Bitroponyls* (e.g., **163**) easily undergo dehydrative cyclization to form furoditropones **164** (Scheme 39; 56MI4; 67TL433) which undergo heterocycle-exchange reactions yielding thieno- and pyrroloditropones **165a-c**. Type **164** furoditropones are also obtained by acid hydrolysis of 7,7'-dimethoxy-2,2'-bitroponyls (67TL433).

The pentacyclic bitroponone **166** is prepared by the condensation of *p*-tropoquinone (**137**) and 1,2,4,5-tetraaminobenzene (88CL175; 89CL1719).

4. From Natural Sources

Some heterocyclic fused derivatives have been found among the great number of troponoids occurring in molds and higher plants [55CRV9, p.22; 56FOR(13)232, p.236; 59MI1, p.347; 73CRV293, p.323; 85HOU(5/2c)710, p.739]. Other examples have been easily obtained from natural precursors.

The furoditroponone, utahin (**162**), was discovered as a constituent of *Juniperus utahensis* (68CC233; 83CL1371). The heartwoods of certain Coniferae owe their resistance to wood-destroying fungi largely to the presence of troponones.

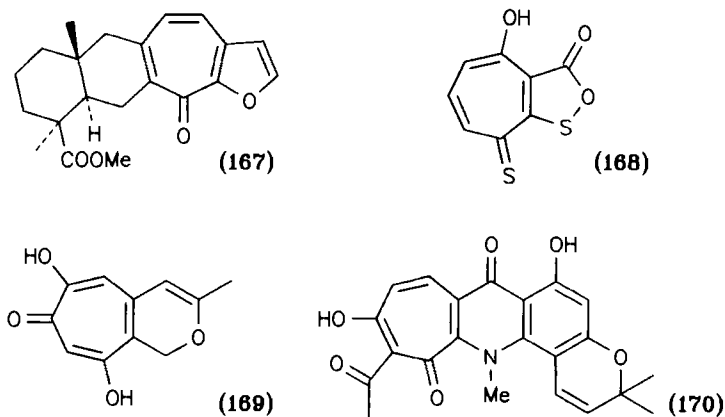
Methyl dehydrohispanonate (**167**, Scheme 40) is prepared by esterification (diazomethane) and dehydrogenation (DDQ) of hispanonic acid extracted from Labiate species *Ballota hispanica* (79JOC2219).

The tropolone alkaloid of Liliaceae species, colchicine, is transformed by acetylation, alkaline cyclization, and dehydration into the tetracyclic pyrrolotropone acetyl anhydrocolchicine [77TL2977; 83AX(C)1709]. When the dicarboxylic acid anhydride groups of puberulonic and stipitatic acids (metabolites of *Penicillium* species) condense with *o*-phenylenediamine, another tetracyclic pyrrolotropone structure is formed (51JCS1139; 59JCS2847).

The interesting [1,2]oxathiolotropothione thiotropocin (**168**) has been obtained from *Pseudomonas* CB-104 (84MI1, 84TL419). The biosynthetic shikimate origin of the antibiotic **168** was elucidated by ^{13}C labeling (92JA8479); the biotechnical production (under the name "troposulfenin") proceeds using cultures of *Pseudomonas troposulfenii* PB-5020 (84JAP59/205994).

Anhydrosepedonin (**169**) was isolated with sepedonin from culture filtrates of the fungus *Sepedonium chrysospermum* (65CJC1835). It is believed to be formed from sepedonin by spontaneous dehydration. On the other hand, it was demonstrated by the ^{14}C tracer method that the metabolite **169** might be biosynthesized through the polyketomethylene pathway (71ABC862). An "antibiotic C" of similar trihydroxy structure is produced by fermentation with *Aspergillus nidulans* (83BRP2113672).

Finally, the homoacridone alkaloids, citropone A (**170**) and similar tricyclic citropone B, were isolated from some cultivated citrus plants (90CPB1881).



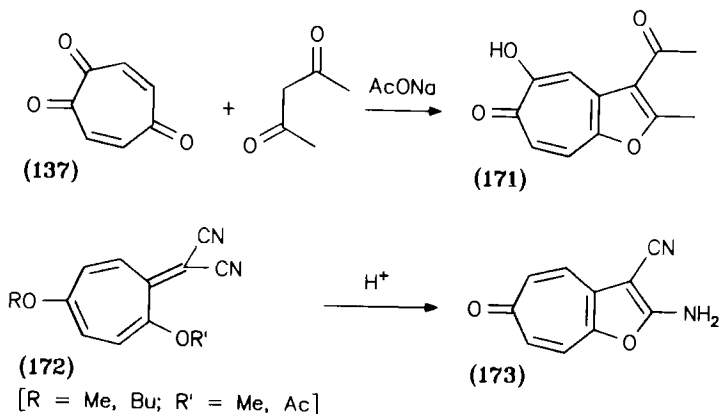
SCHEME 40

B. SYNTHESSES OF TROPONES AND TROPOLONES FUSED TO INDIVIDUAL HETEROCYCLIC RINGS

(As a rule, general syntheses mentioned in Section II,A will not be repeated here, but they are listed in Table IV.)

TABLE IV
GENERAL TROPONOID SYNTHESSES REVIEWED IN SECTION II,A

Fused heterocycle	Subsections in Section II,A	Tables	Formulas
furan	1a,c,d; 2a-c; 3a-d,i,k; 4	I-III	6, 11a, 30, 31, 48a, 53a, 58, 60, 62, 73, 100, 104, 107, 154, 159, 162, 164, 167
thiophene	1a,c,d; 2a-c; 3k	I,II	8, 9, 11b, 29, 32, 33, 36, 48b, 51, 65, 70, 165a
[1,3]dithiole	2a	II	
[1,2]oxathiole	4		168
selenophene	2b		48c
pyrrole	1a,b,d; 2a-c; 3c,d,f,j,k; 4	I,II	39, 46, 53b, 56, 101, 109, 125-129, 157, 165bc
pyrazole	1b,d; 2a,b; 3b-d	I,II	79b, 81, 83, 85-87, 89, 98, 110, 142, 143
imidazole	1b-d; 2a; 3d,g	II	15, 16, 19, 24c, 105, 133
triazole	1d; 2a; 3d,g,h	II	111, 134, 145, 147
indolizine	2b		
isoxazole	1a; 3b,c,h		10b, 79a, 90, 91, 148
oxazole	1c; 3c,e-g	I	24a, 93, 114, 131
oxadiazole	1d		
thiazole	1c		24b
thiadiazole	3h	II	149
pyran	3b; 4		76, 78, 169
thiopyran	2c		67, 68
pyridine	1a,b; 2a,b; 3h; 4	I,II	13, 43, 152, 170
pyridazine	3c		102
pyrimidine	3c		94
pyrazine	1d; 3e,g,k	II	27, 118c, 166
triazine	3g		140
oxazine	1b; 3e		22, 118a
thiazine	1b; 3e-g		118b, 121, 123, 136
oxepine	3h,i		147b, 156a
azepine	3i		156b
diazepine	3c		95
Fe complex	1c; 2a	II	
Cr complex		II	

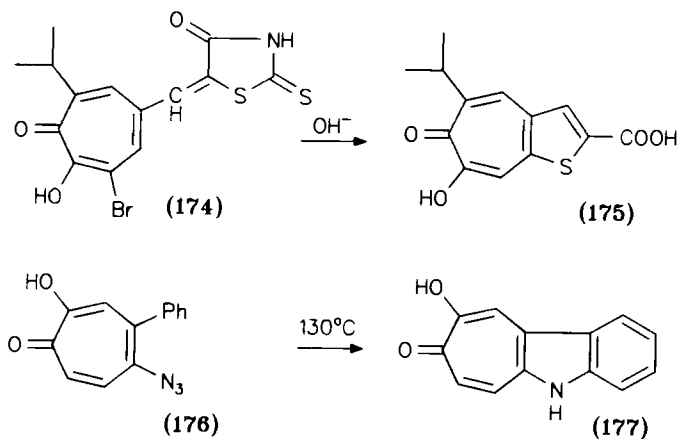


SCHEME 41

1. Five-Membered Rings

a. *Furans*. Special examples of heterocyclization (Scheme 41) cover the reaction of acetylacetone carbanion with *p*-tropoquinone (**137**) to yield tropolone **171** (76TL2339) and the acid hydrolysis of substituted 8,8-dicyanoheptafulvenes **172** that unexpectedly gave furotropone **173** (91MI2).

b. *Thiophenes*. Rhodanine derivative **174** (Scheme 42) is available from the corresponding tropolone carboxaldehyde. On treatment with alkali, it

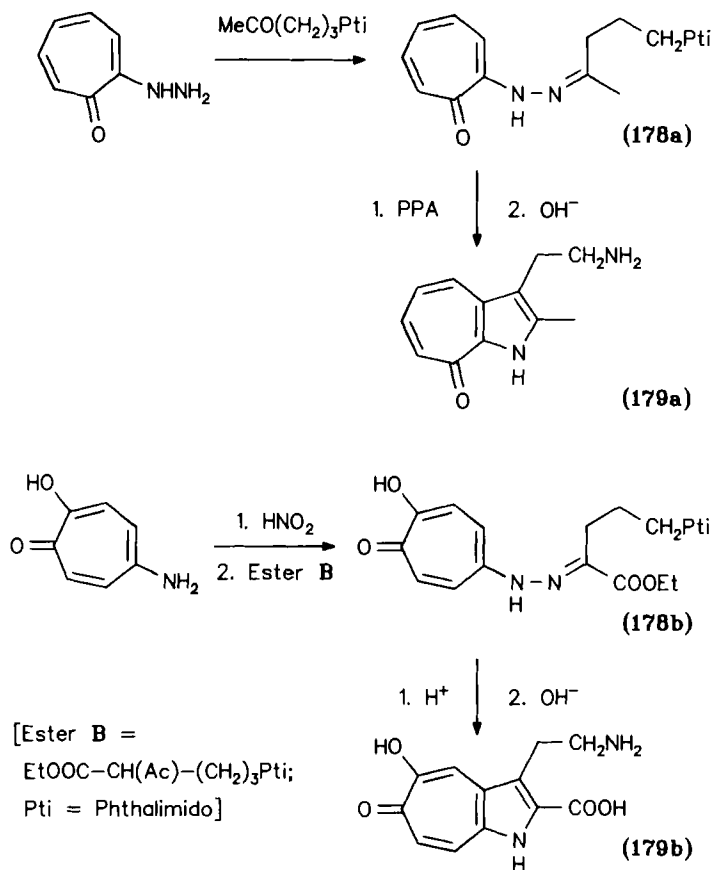


SCHEME 42

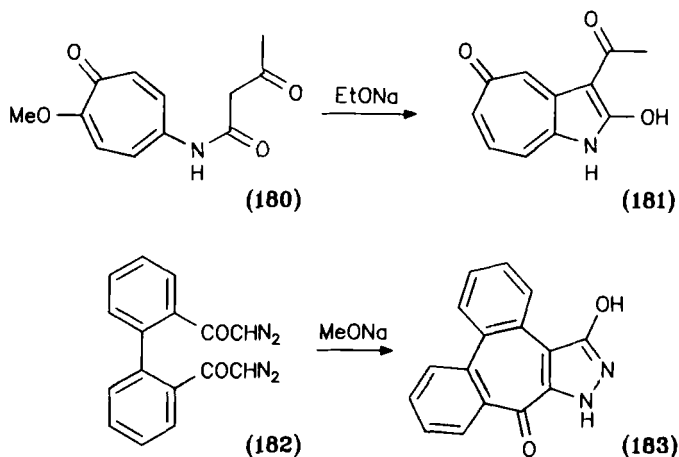
rearranges to yield thienotropolone **175** (62BCJ808). The reaction presumably proceeds by the opening of the rhodanine ring, followed by the intramolecular attack of the sulfide anion at the tropolone C-4, with the liberation of the bromide ion from C-3 (cine substitution; cf. Section II,B,1,f).

c. *Pyrroles*. Several specific routes are available for pyrrolo- and indolotropolones. Thus, thermal decomposition of azidotropolone **176** gives indolotropolone **177** (Scheme 42), obviously proceeding through the *nitrene intermediate* (72BCJ226).

Moreover an equivalent of the *Fischer indolization* of hydrazones proved to be a versatile method of the pyrrolotropone and -tropolone synthesis. Hydrazones like **178a** (prepared from 2-hydrazinotropolones and carbonyl



SCHEME 43



SCHEME 44

compounds) cyclize to form cyclohepta[*b*]pyrrol-8-ones (type **179a**, Scheme 43).

On the other hand, the *Japp-Klingemann reaction* of diazotized 5-aminotropolones and CH-acidic methylene compounds provides precursors (e.g., **178b**) of 5-hydroxycyclohepta[*b*]pyrrol-6-ones (type **179b**). The examples given in Scheme 43 depict syntheses of seven-membered-ring analogs (**179a,b**) of natural products, tryptamine and serotonin, respectively (67CPB634; 63CPB1440, resp.).

Further syntheses of **179a**-type tropones pass through the troponylhydrazones of aldehydes and open-chain ketones (54MI2; 61YZ1799) or cyclic ketones and piperidones (62YZ408; 75BCJ314). Pyrrolotropones having no substituent at C-3, however, are formed in extremely low yields by this reaction (69MI1). Starting from 2-hydrazino-7-methoxytropone and propionaldehyde, a Fischer reaction with subsequent ether cleavage yields the corresponding pyrrolotropone (63MI1). The pyrrole rings of **179b**-type tropolones are cyclized using 2-alkylacetoacetates and 2-acetylsuccinates (62YZ414; 63CPB1431) or 2-formylcycloketones (74BCJ1951).

An additional route to pyrrole ring annulation includes the unusual intramolecular attack at C-6 of the *diketene adduct* **180** (Scheme 44) that forms pyrrolotropone **181** bearing the carbonyl group in the rare β position (65BCJ306, 65MI2; 67MI1; 73CRV293, p.352). Furthermore, indolotropones occur as the 3,*o*-type rearrangement by-products from the benzidine-type rearrangement of 2-(arylhydrazino)tropolones (89BCJ128).

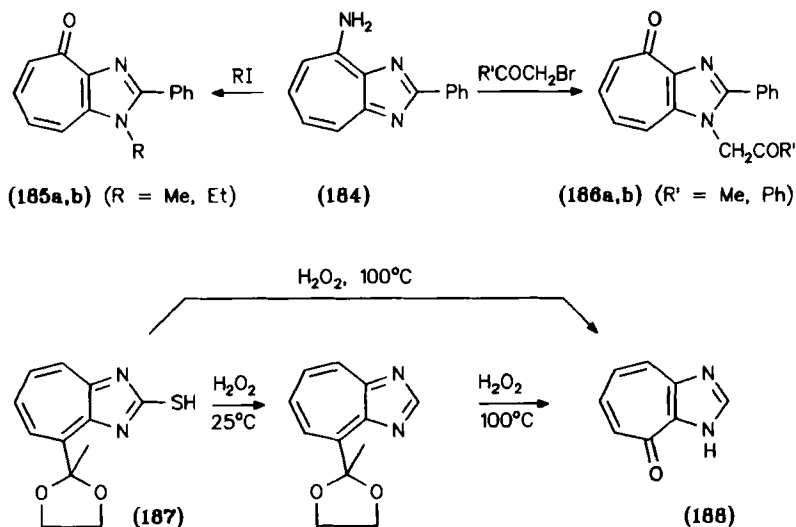
Recently, cyclohepta[*b*]pyrrol-4-one derivatives were obtained as by-products in the 1-azaazulene synthesis from 2-chlorotropone and 1-(diphenylphosphinyl)azaallyl anions [93H(36)2247].

Pyrrolotropone is formed by a thermal *retro-Grignard reaction* from a 4-aryl-4-hydroxycyclohepta[*b*]pyrrole derivative (72CB1224). Finally, cycloadditions of 8-styryl-1-azaazulenes with dimethyl acetylenedicarboxylate and subsequent oxidation yield 1,7-ansa-bridged pyrrolotropones (80BCJ1406).

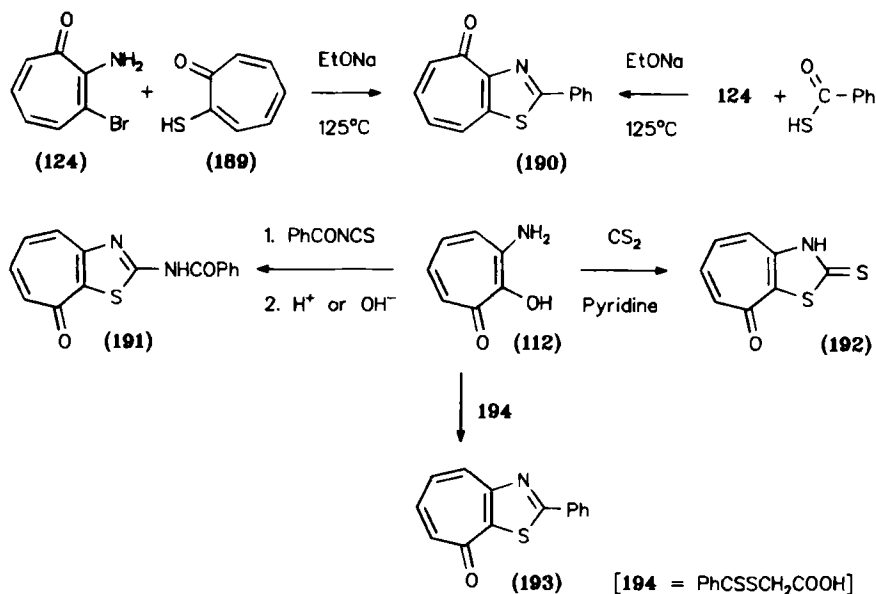
d. *Pyrazoles*. Both tropone and heterocyclic rings are cyclized on treatment of bisdiazoketone **182** with base to yield pyrazolotropone **183**, as shown in Scheme 44 [82IJC(B)765].

e. *Imidazoles*. When 1,3-diazaazulene **184** reacts with alkyl iodides or α -bromoketones, these reagents attack at N-1, and the amino group is hydrolyzed to give imidazotropones **185** and **186** in low yields (Scheme 45; 92JHC1219). Desulfurization of another 1,3-diazaazulene derivative (**187**) by hydrogen peroxide affords unsubstituted imidazotropone **188** (90JHC887).

f. *Thiazoles*. The first attempts to obtain thiazolotroponoids from tropenyl thiosemicarbazide or tropolonyl thiourea derivatives failed (59MI2). Soon thereafter, Nozoe *et al.* (62BCJ2003) unexpectedly obtained thia-



SCHEME 45



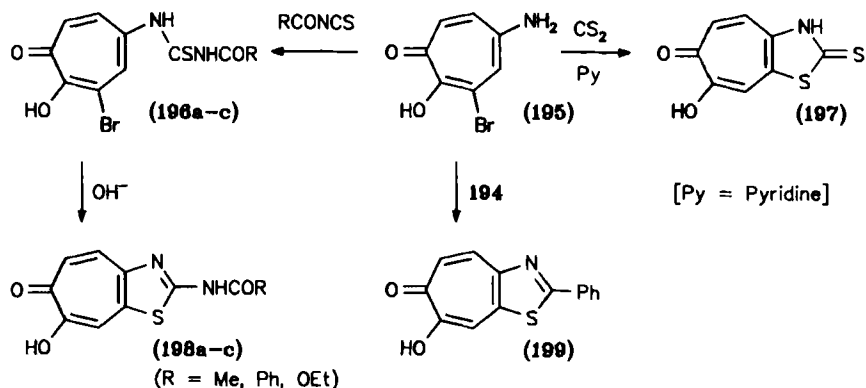
SCHEME 46

zolitropones (e.g., **190**; Scheme 46) from the condensation of 2-amino-3-bromotropones (**124**) with 2-mercaptotropones (**189**). The structure of tropone **190** was confirmed by its independent formation from **124** and thiobenzoic acid. Since tropone **189** proved stable under the actual reaction conditions, its condensation with **124** was presumed to involve the initial formation of a bitroponyl thioether that underwent rearrangement.

On the other hand, Seto and Ogura (64BCJ1526) prepared isomeric thiazolotropone **193** as well as the 2-amino (**191**) and the 2-mercapto derivatives (**192**) from 3-aminotropolone (**112**) and dithiobenzoate **194**, isothiocyanate, or carbon disulfide, respectively.

Analogously, thiazolotropolones **197–200** (Schemes 47 and 48) arise from similar condensations of 5-amino-3-bromo- or 5-aminotropolones (**195, 203**) with dithioesters **194** and **201**, isothiocyanates, or carbon disulfide, respectively (62BCJ1998; 63BCJ173; 64BCJ1526, 64JAP64/10132).

These cases of anomalous nucleophilic substitution of bromine at C-3 by substituents entering position 4 of the tropolone rings (in **195, 196**, and **202**) belong to the field of "*cine substitution*." This term means the introduction of a new substituent at a site different from that occupied by the group displaced (71PAC239, p.247; 79ACR132; 84MI2, pp.97, 117; 85MI4, p.156).

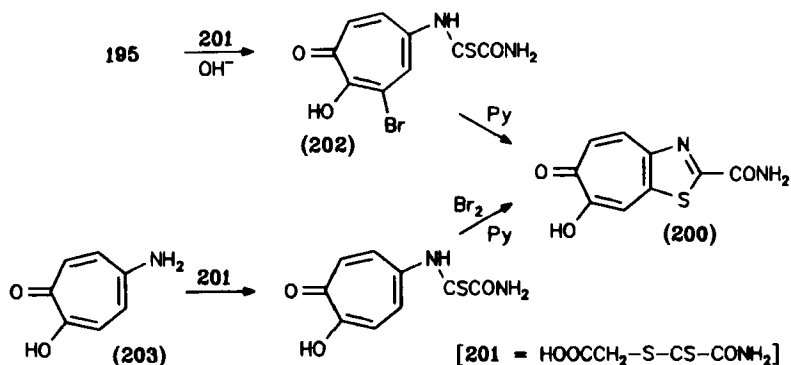


SCHEME 47

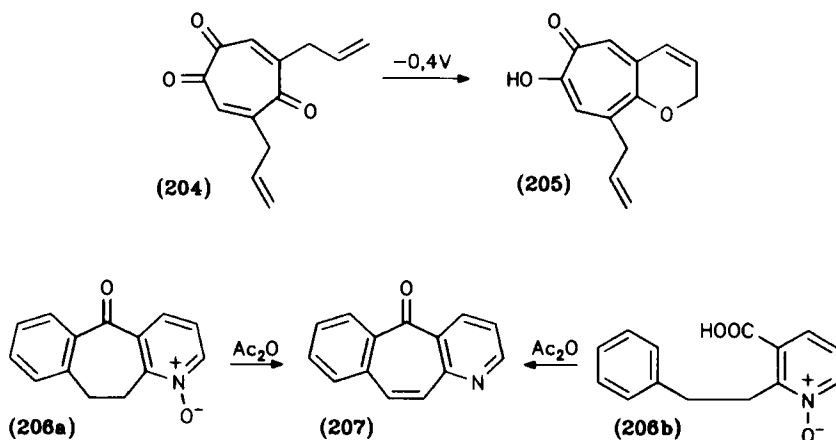
In troponoid chemistry cine substitution occurs frequently. In many cases it can be explained by the intermediacy of dehydrotropolone species ("tropononyne") as trapped, for example, by azides (Section II,A,3,h; Scheme 34). An alternative mechanism may be a Michael-type addition followed by elimination. The intramolecular cyclizations depicted in Scheme 47 very likely proceed via Michael-type attack (73CRV293, p.351).

2. Six-Membered Rings

a. *Pyrans*. When 4,6-diallyl-*p*-tropoquinone (**204**, Scheme 49) was electrolyzed, the formation of pyranotropolone **205** was detected (87BCJ1747).



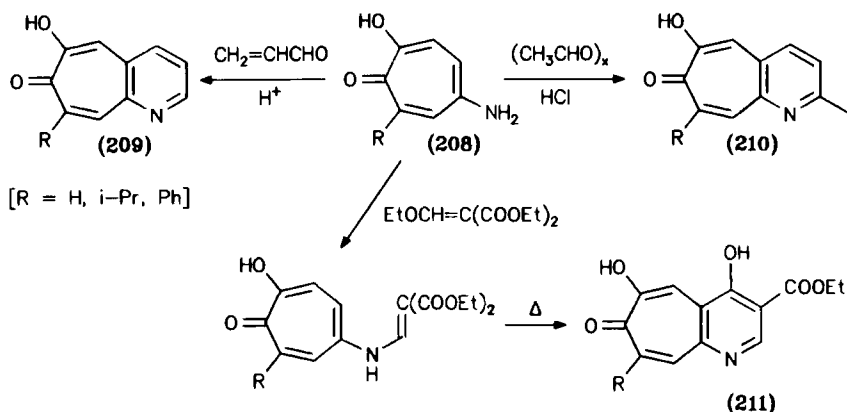
SCHEME 48



SCHEME 49

b. *Pyridines*. Dehydrogenation of fused cycloheptadienones (Section II,A,1,a) or their open-chain precursors to afford pyridotropones (e.g., **207**) can be achieved by the acetic anhydride rearrangement of corresponding *N*-oxides **206a** or **206b**, respectively (67USP3357986).

The *Skraup*, *Doebner–Miller*, and *Gould–Jacobs reactions* for the syntheses of quinolines, quinaldines, and 4-hydroxyquinolines, respectively, were applied to 5-aminotropolone derivatives (e.g., **208**, Scheme 50) to get pyridotropolones **209–211** (59NKZ75; 68NKZ620) and other derivatives [52CI(L)471; 60NKZ295]. These reactions illustrate the behavior of 5-aminotropolones as typical aromatic amines (55CRV9,



SCHEME 50

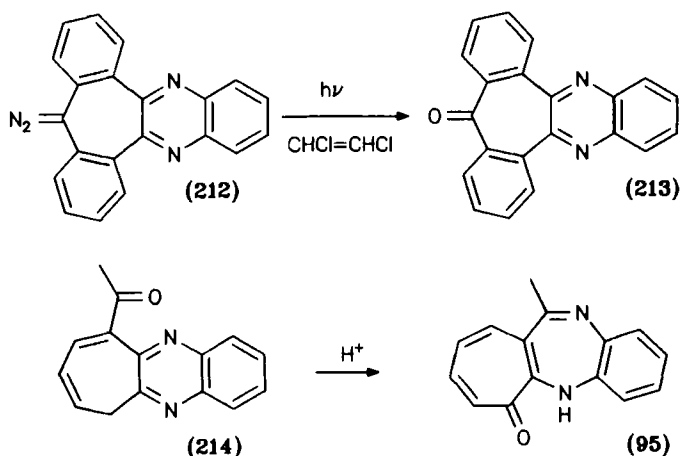
p. 98). 4-Aminotropolone gives analogous products, for example, **296** (59MI4).

The Skraup-type reactions proceed by the use of acrolein or 2-bromoacrolein in the presence of mineral acids or with glycerol and sulfuric acid [52CI(L)562; 60NKZ509]. The quinaldine-type products are afforded by acetaldehyde, crotonaldehyde, or paraldehyde in the presence of hydrochloric acid (54JCS286).

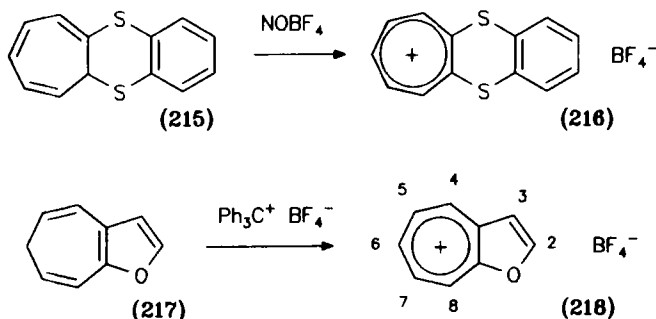
The 4-hydroxypyridine (or 4-pyridone) derivatives are obtained by the use of ethoxymethylenemalonate and acetoacetate (59NKZ534) or acetylenedicarboxylate (78USP4130649). In analogy to these reactions, cyclizations starting from 5-aminotropolone ethers (83USP4382088) or 2-aminotropones (83USP4381304) were claimed.

c. *Pyrazines*. In a photochemical reactions, a nucleophilic carbene is generated by irradiating the diazo compound **212** (Scheme 51); in the presence of 1,2-dichloroethylene, the carbene forms quinoxalotropone **213** and the corresponding azine [81JCR(S)178]. 2,3-Dihydropyrazinotropones are dehydrogenated by DDQ [83H(20)1117].

d. *Benzo[1,4]oxazines and -thiazines*. The complicated chemistry of seven-membered-ring fused benzazines ("benzotropazines") has been summarized in easily accessible reviews by Nozoe [82PAC975; 90H(30)1263; see also 83MI1]. Reported synthetic aspects, apart from those mentioned in Section II,A (Table IV), relate to benzoxazinotropones [78BCJ3316; 85BCJ2840; 89H(29)1005] and benzthiazinotropones (66BCJ1980;



SCHEME 51



SCHEME 52

85BCJ165). These will not be repeated here in detail, but the features of their chemical behavior will be covered in Section II,D,2.

3. Seven-Membered Rings

Another example of ring transformation is the preparation of benzodia-zepinotropone **95** (Section II,A,3,c) from quinoxaline **214** in the presence of acid (79MI3; 81JHC335).

C. GENERAL SYNTHESES OF HETEROCYCLIC FUSED TROPYLIUM SALTS

1. From Other Seven-Membered-Ring Compounds with Fused Heterocyclic Rings

a. *From Cycloheptatriene Derivatives by Hydride Abstraction.* This reaction is one of the most common routes. Among inorganic oxidants, phosphorus pentachloride and nitrosyl tetrafluoroborate are used to obtain azolotropylum salts **23a–c** (Scheme 6) from tropilidenes **25a–c** (67CPB619) or to prepare dithiinotropylum salt **216** (Scheme 52) from **215** (88BCJ271), respectively.

The Dauben reaction, i.e., hydride exchange between cycloheptatrienes and triphenylcarbenium salts, is by far the most popular synthetic method in this field [67UK1721, p.1745; 72HOU(5/1d)301, p.395; 73CRV293, p.312; 73MI2, p.1586; 85HOU(5/2c)49, p.55]. For example, hydride transfer from furotropilidene **217** affords furotropylum salt **218** (80TL3375).

Further reactions following this scheme are listed in Table V. 4-Alkoxy-5-halo-8*H*-cyclohepta[*b*]thiophenes resist hydride exchange (73JOC146).

TABLE V
HETEROCYCLIC FUSED TROPYLIUM SALTS FROM CYCLOHEPTATRIENES
AND TRIPHENYLCARBENIUM SALTS (SCHEME 52)

Fused heterocycle ^a	Further fusion or substitution ^b	Reference
furan	2-Me-3-Ac ^c	77BCJ3425
	2,3-benzo ^d	81AJC1037
	2,3-tropilideno	88TL4723
thiophene	—	77S268
	2,3-benzo ^d	81AJC1037
	4,5-thieno and 7,8-thieno	78T587
isoxazole	3-aryl	86CL1925
cyclobutadiene-Fe(CO) ₃	—	78AJC1607

^a [b]Fusion as given in formula **218** throughout the table.

^b The numbering is that used for the bicyclic system, e.g., **218**.

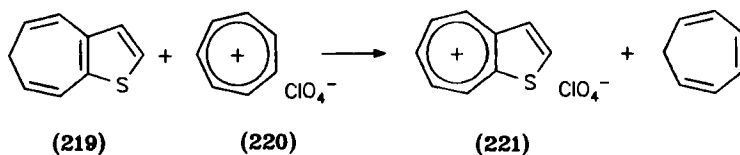
^c The precursor was formed by base-catalyzed cyclization of the (diacetylmethyl)tropylium salt.

^d The precursors were obtained from a mixture of several isomeric cycloheptatrienes formed from 2-phenoxy- or 2-phenylthiophenyl carbenes by intramolecular carbene insertion.

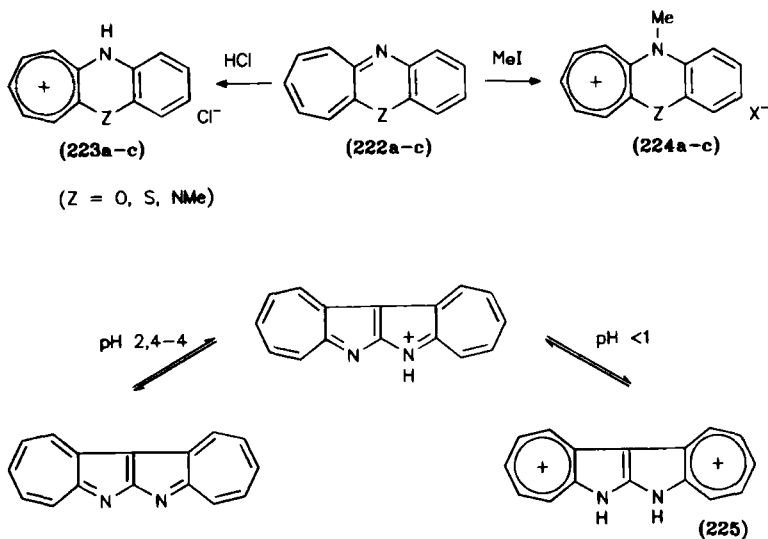
The use of tropilidenes obtained by reduction of tropones or by cyclization of nonfused tropylium salts is dealt with in Sections II,C,1,c and II,C,3,a, respectively.

Along with the triphenylcarbenium ion, any carbenium ion sufficiently less stable than the tropylium ion product can abstract hydride from the corresponding tropilidene. Even less stable tropylium ions can do this. Thus, the more stable (less electrophilic) thienotropylium salt **221** is formed from **219** or its isomers at the cost of tropylium salt **220** (Scheme 53; 63TL401). By means of such reactions [68ZOR907; 69ZOR1135; 71JOM(33)195], ranges of decreasing stabilities were found (Section III,B,3,b).

b. *From Cycloheptatriene Derivatives by N-Protonation or N-Alkylation.* Benzazinetropylium salts (**223a–c**, **224a–c**) are prepared from the corres-



SCHEME 53



SCHEME 54

ponding cycloheptabenzazines **222a-c** by, respectively, protonation with hydrogen chloride and methylation with methyl iodide or trimethyloxonium tetrafluoroborate (Scheme 54; 88BCJ271; 89BCJ1158). Furthermore, **222a,b** and derivatives are protonated by trifluoroacetic acid and methylated by "magic methyl" CH_3OSO_2F to give similar species in solution (78BCJ-2185, 78BCJ3316; 79BCJ3123; 85BCJ165).

1,3-Diazaazulene is similarly alkylated (65CPB810). Other examples of *N*-protonation relate to pyrrolo- and indolotropylium ion (68BCJ2102, 68BCJ3027), indenopyrrolotropylium ion [89H(29)1655], bispyrrolotropylium ion **225** in solution (93TL835), diazepinotropylium salt **345** (81JHC335), and the work of Nozoe *et al.* on protonation (78BCJ2185; 89BCJ1158), cyclization, and heterocycle exchange in the field of benzotropazines (Section II.D,2).

c. From Tropones by Reduction or Organometallic Addition. According to El'tsov *et al.*, Guillard *et al.*, El Borai *et al.*, and other authors, fused tropones can be transformed into tropylium salts by a two-step route: reduction (Table VI) or organometallic addition (Table VII), both followed by acid-catalyzed dehydration. An example is that of thieno- or pyrrolo[c]-tropylium salts **228** and **230** (Scheme 55; 68ZOR907). In many cases the intermediate tropol derivatives (pseudobases such as **227**, **229**) were nonisolable or, at least, unstable.

TABLE VI
HETEROCYCLIC FUSED TROPYLIUM SALTS BY REDUCTION OF TROPONES

Fused heterocycle ^a	Position of CO ^b	Further fusion or substitution ^b	Reagent for reduction	Reference
[b]furan	6	Me		71CR(273)160
		Me	LiAlH ₄ ^c	77BSF(2)75
		5,7-(CH ₂) ₈ ^d	LiAlH ₄ ^c	85MI3
[b]thiophene	6	Me	LiAlH ₄ ^{ce}	71BSF1437
[c]thiophene	6	Me, OMe	LiAlH ₄ ^c	67ZOR191
		Me	LiAlH ₄ ^c	69ZOR570
		Me		69ZOR2072
		Me	NaBH ₄ , LiAlH ₄	71BSF1437
		Me, Br	NaBH ₄	74YZ1429
		Me	LiAlH ₄	70ZOB2078
[c]pyrrole	8	Me	LiAlH ₄ ^c	69ZOR570
	6	Me	LiAlH ₄ ^c	69ZOR2072

^a [b] And [c] fusion as given in formulas **221** and **228**, respectively.

^b The numbering is that used for the bicyclic system, e.g., **228**.

^c The tropol derivative (e.g., **227**) was not isolated.

^d Ansa compound.

^e The reduction by NaBH₄ was incomplete.

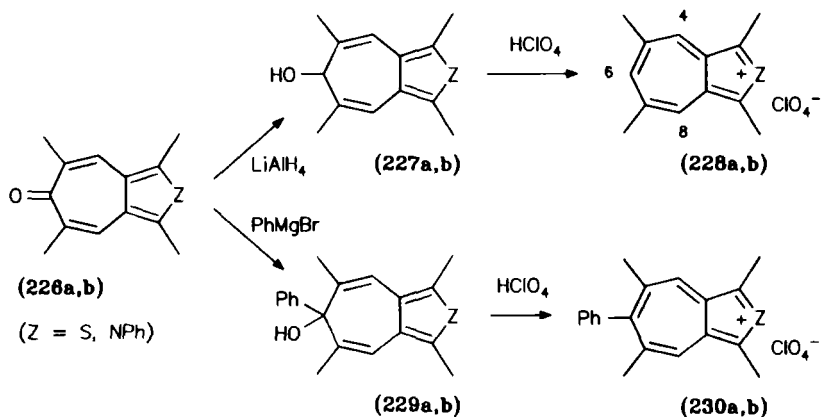
TABLE VII
HETEROCYCLIC FUSED TROPYLIUM SALTS BY ORGANOMETAL ADDITION ONTO TROPONES

Fused heterocycle ^a	Position of CO ^b	Further fusion or substitution ^b	Reagent for addition	Reference
[b]furan	6	Me	MeLi, PhLi ^c	85MI1
[c]furan	6	Me	MeLi, PhLi ^c	85MI1
[b]thiophene	6	Me	MeMgI ^c	81MI1
[c]thiophene	6	Me	MeMgI ^c	81MI1
		Me, Cl	PhLi	67JOC1610
		Me	PhLi	74YZ1429
[b]pyrrole	4	2,3-diphenyl-	PhLi, PhMgBr	72CBI224
		5,6; 7,8-dibenzo-		
oxazole	4	7,8-dibenzo	1-Mc-4-piperidyl-MgCl ^d	74JMC1316

^{ab} See Table VI.

^c The tropol derivative (e.g., **229**) was not isolated.

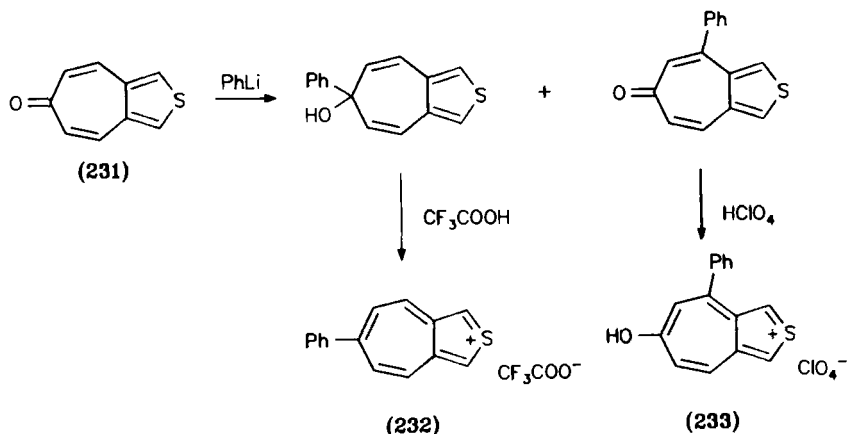
^d Tropylium salt only in solution.



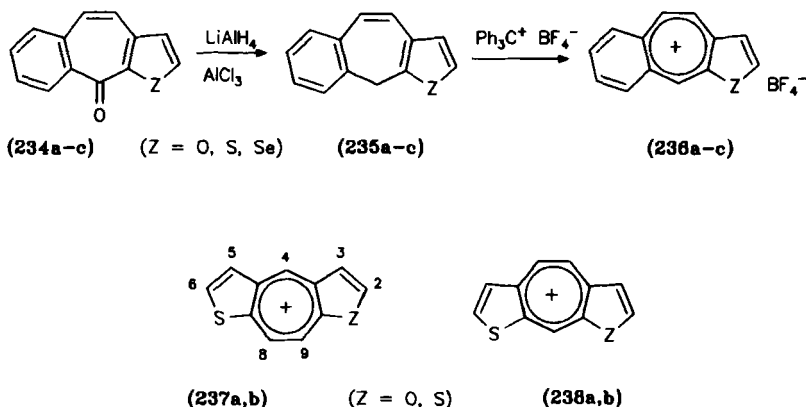
SCHEME 55

Some unexpected reactions are observed during the interaction of cyclohepta[c]thien-6-one (**231**) or its 1,3-dibromo derivative and organometallic compounds (74YZ1429): These reactions are halogen-metal interconversion and subsequent dimerization, partial debromination, and simultaneous 1,2- and 1,4-addition of phenyllithium onto tropone **231** to yield tropylum salts **232** and **233**, respectively (Scheme 56).

In the presence of aluminum chloride, tricyclic tropones **234a-c** (Scheme 57) are easily reduced by complex hydrides to exceed the tropol stage and to afford tropilidenes **235a-c**. Hydride abstraction (Section II,C,1,a) leads to tropylum salts **236a-c**, but **236a** could not be obtained in pure form [83CS(22)53].



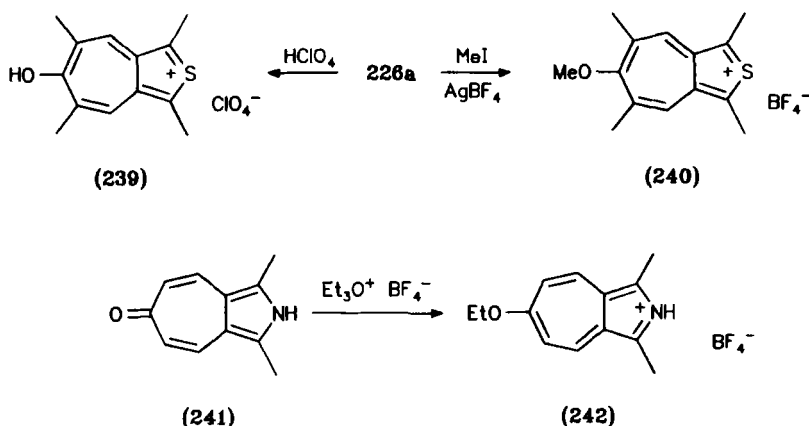
SCHEME 56



SCHEME 57

According to further papers from Gronowitz *et al.* [70ZC389; 73ACS2257, 73CS(3)165; 78JHC285], the reduction of other tricyclic tropones does not require the presence of a Lewis acid. This might be due to the stability (see Section III,B,3,b) of the carbenium ions (formed from the intermediate tropols), which are further reduced to the tropilidenes by hydride transfer. For example, tropylium ions **237** and **238** can be prepared by this method.

d. *From Tropones by Protonation or Alkylation.* Tropones (e.g., thieno[c]tropone **226a**) are protonated or alkylated at the oxygen atoms to form hydroxy- (**239**) or alkoxytropylium salts (**240**), respectively (Scheme



SCHEME 58

58; 68ZOR907; 69ZOR961). Structure **239** replaces that of the bimolecular ionic associate as published earlier (67ZOR191).

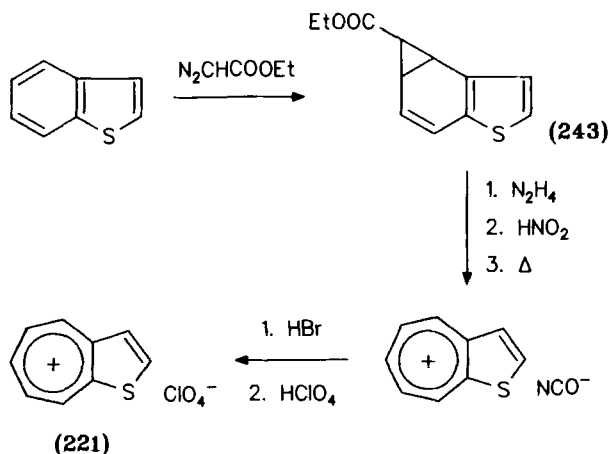
Other examples of *O*-protonation relate to tropones fused onto thiophene (74YZ1429), triazole (e.g., **111**; 71CB1573), oxepines or azepines (e.g., **156a,b**; 88CL1647; 90CL91; 92TL6487), and tricarbonyl cyclobutadieneiron (78AJC1607; see Section II,E,1). Solutions of tropones in strong acids (trifluoroacetic acid or concentrated sulfuric acid) often exhibit the tropylium ion structure of the solute [66JCS(C)926; 67JOC1610; 70JA6382; 75TL1849; 80BCJ1461; 88CL175].

An important method of tropone *O*-alkylation consists of the use of trialkyloxonium tetrafluoroborate (70JA6382). Thus, violet azaazulenium salt **242** can be obtained from "vinylous carboxamide" **241** by selective alkylation (75AG840).

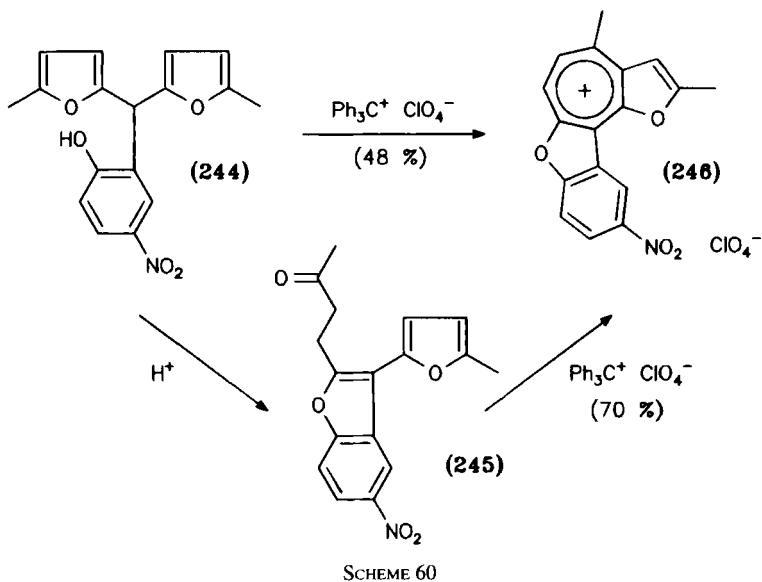
N-Alkylation (quaternization) of oxazolotropone **114b** (63UP1) or thiazolotropone (64UP1) and -tropone (66UP1) also causes bathochromic shifts that are presumably due to the participation of tropylium structures (see Section IV,A,5,a). The contribution of (polar) tropylium forms is also likely in the case of heterocyclic fused sesquifulvalenes that have been obtained from the corresponding tropones (Section IV,A,4,c).

2. By Reactions Forming the Seven-Membered Ring

The Dewar-Pettit method of ring expansion was applied to the synthesis of thienotropylium salt **221** from thionaphthene via norcaradiene derivative **243** and isomers (Scheme 59; 63TL401; 64JA5630).



SCHEME 59

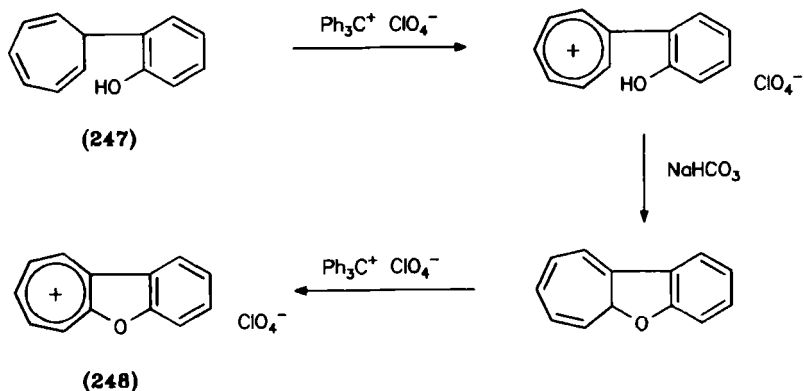


SCHEME 60

A remarkable formation of difurotropylium salt **246** (Scheme 60) proceeds by hydride abstraction from **244**, furan ring cleavage, and recyclization or similarly via intermediate **245** (92KGS1142).

3. By Reactions Forming the Heterocycle

a. *From Cycloheptatriene or Nonfused Tropylium Derivatives.* Tropilidenes bearing a properly *o*-substituted phenyl group offer a route



SCHEME 61

to benzofuro- or indolotropylium salts [85HOU(5/2c)49, p.57]. Thus, *o*-hydroxy- (or *o*-acetoxy-) phenyltropilidenes such as **247** (Scheme 61) undergo a sequence of hydride abstraction, cyclizing deprotonation, and another hydride abstraction to give tricyclic tropylium salts **248** [66JCS(C)926; 67BCJ1480; 71JCS(C)2399].

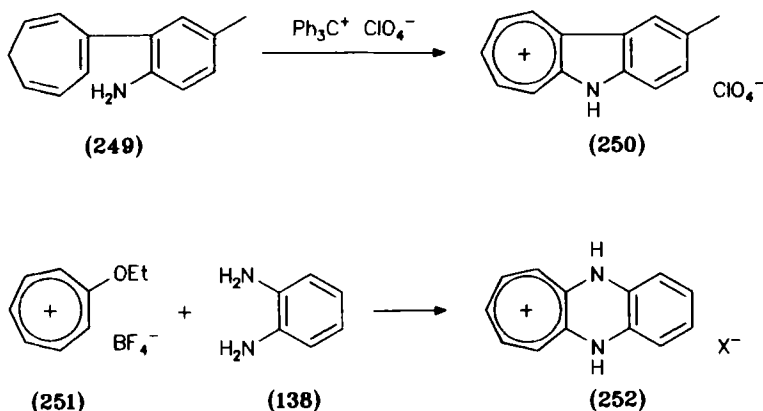
In a similar reaction, *o*-tropyltoluidine **249** yields tropylium salt **250** (Scheme 62; 68BCJ3027).

According to Fukunaga (cf. 73MI1, p. 223; 89BCJ1158), the condensation of ethoxytropylium salt **251** with *o*-phenylenediamine (**138**) gives quinoxalotropylium salt **252** or its mesomers (see Section III,B,3,a). (For other benzazinetropylium derivatives, see Section II,D,2.)

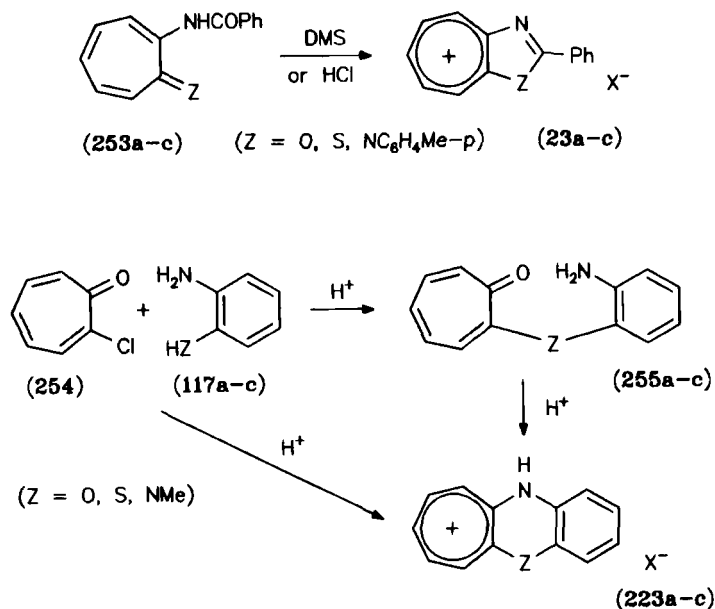
b. *From Tropones.* 2-Benzazidotropones, -tropothiones, and -troponeimines (**253a–c**, Scheme 63) can be cyclized by means of dimethyl sulfate (DMS) or hydrochloric acid to provide azolotropylium salts **23a–c** (66NEP6660777; 67CPB619, 67FRP1491800).

Tropones (e.g., **254**) bearing an eliminative group at C-2, together with anilines **117a–c**, cyclize in an acid medium to give benzazinetropylium salts **223a–c** (85BCJ165; 89BCJ1158, 89JAP01/211572; cf. Section II,D,2). Intermediates **255a–c** yield the same products.

c. *By Transformations of Heterocyclic Rings.* 2-Phenyl-6-amino-6H-cycloheptoxazole derivatives (**256**) give tropylium salts **23c** by a reaction with *p*-toluidine (Scheme 64; 67CPB627). (For benzazinetropylium salts, see Section II,D,2.)



SCHEME 62



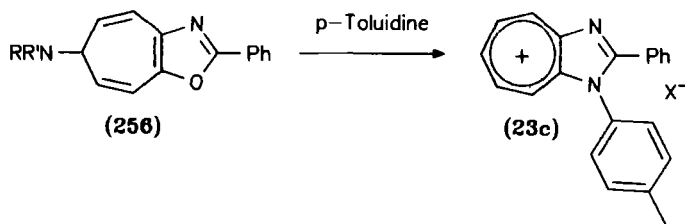
SCHEME 63

D. SYNTHESIS OF TROPYLIUM SALTS FUSED TO INDIVIDUAL HETEROCYCLIC RINGS

(General syntheses dealt with in Section II,C are listed in Table VIII.)

1. Five-Membered Rings

a. *Furans*. Tricyclic tropylium (258 in solution) and bitropylium salts (260, Scheme 65) are prepared by protonation of furan 257 at C-2 (89JHC365) or by cyclization of bitropone 259 with triflic anhydride (85CC1547), respectively.



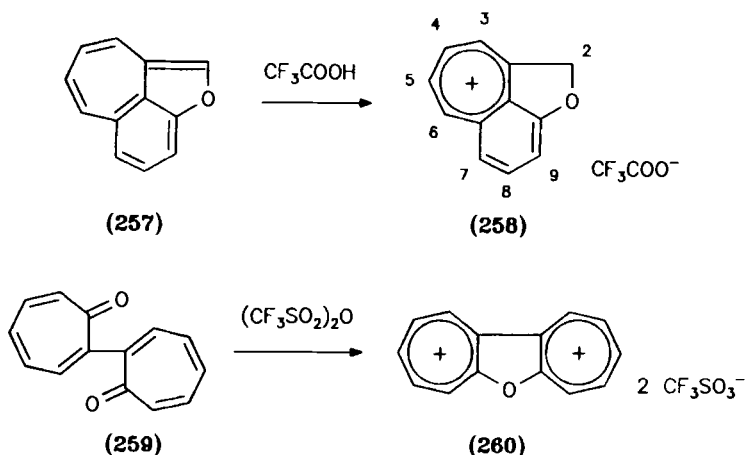
SCHEME 64

TABLE VIII
GENERAL TROPYLIUM SYNTHESIS REVIEWED IN SECTION II.C

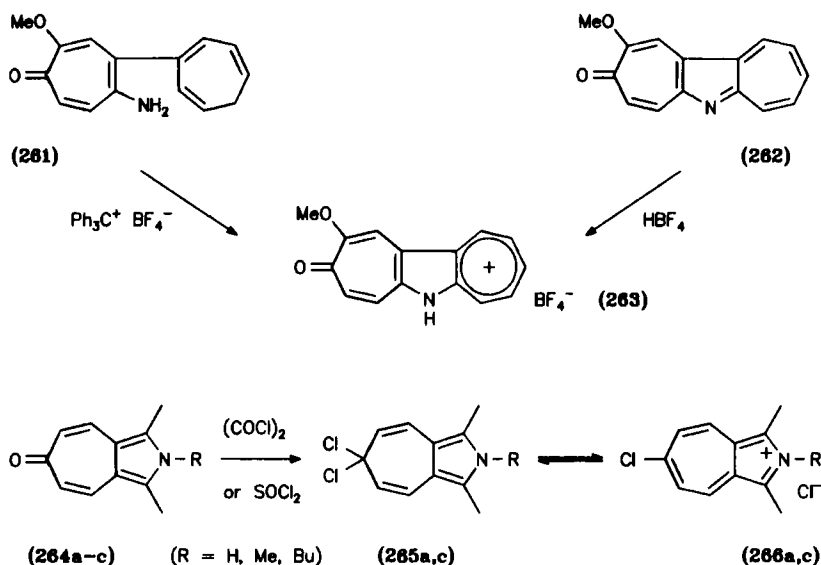
Fused heterocycle	Subsections in Section II.C	Tables	Formulas
furan	1a,c; 2; 3a	V-VII	218, 236a, 237a, 238a, 246, 248
thiophene	1a,c,d; 2	V-VII	221, 228a, 230a, 232, 233, 236b, 237-240
selenophene	1c		236c
pyrrole	1a-d; 3a	VI	225, 228b, 230b, 242, 250
pyrazole	1d		
imidazole	1a,b; 3b,c		23c
triazole	1d		
isoxazole		V	
oxazole	1a,c,d; 3b		23a
thiazole	1a,d; 3b		23b
dithiine	1a		216
pyrazine	1b,d; 3a,b		223c, 224c, 252
oxazine	1b; 3b		223a, 224a
thiazine	1b; 3b		223b, 224b
oxepine	1d		
azepine	1d		
Fe complex	1d	V	

b. *Pyrroles*. Tropylium compound **263** (Scheme 66) can be obtained both on hydride abstraction from tropilidyltropone **261** and on protonation of azaazulenotropone **262** (75TL1849).

By the application of Schönberg's method, pyrrolotropones **264a,c** are transformed into dichlorides **265a,c** and their tautomeric salts **266a,c**



SCHEME 65



SCHEME 66

(79CB2087; 84S119). Chlorocycloheptapyrrole tautomerizes in a similar manner (69ZOR2072).

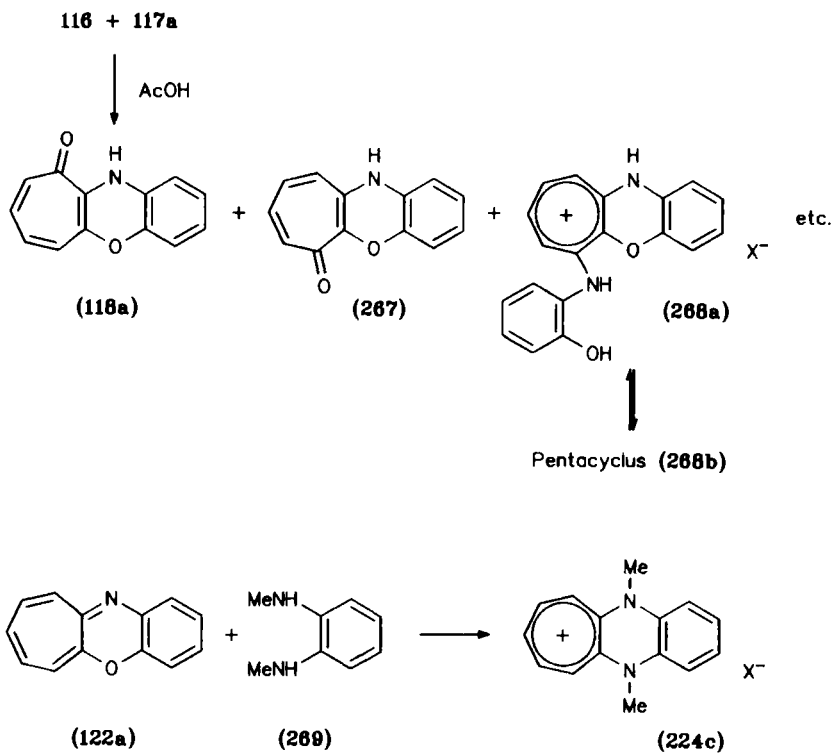
c. *Pyrazoles*. A synthetic approach to the 1,2-diazaazulene system based on the dehydration of 6-hydroxycycloheptapyrazole (Section II,C,1,c) failed as a result of the stability of the cation produced and the presence of a nucleophilic annular nitrogen atom. Thus, the intermediate dimerized to form a pentacyclic bitropylium salt [72JCS(P1)1623].

2. Six-Membered Rings: Benzazines

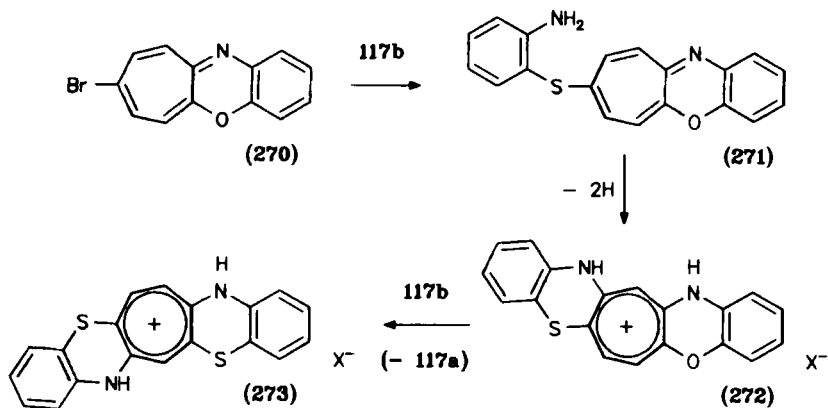
The chemistry of cycloheptabenzazines (see Section II,B,2,d) was reviewed by Nozoe [82PAC975; 83MI1; 90H(30)1263]. In addition to the tropylium syntheses mentioned above (Table VIII), further synthetic pathways (Schemes 67–70) profit by certain interesting, unprecedented properties of the substances involved [83BCJ2756; 88CL1589, 88CL1593; 89BCJ2307, 89H(29)1005, 89H(29)1459].

Characteristic features of the extremely complex reactions are the following:

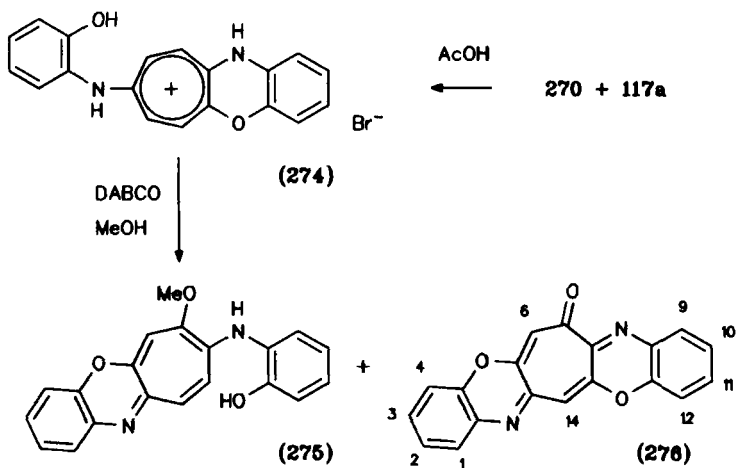
- (a) competitive possibilities for ring closure (see **118a**, **267**) between aniline derivatives (e.g., synthons **117a–c**, **138**, or **269**) and bifunctional or higher-functional tropones (e.g., **116**, **119**, or **120**),



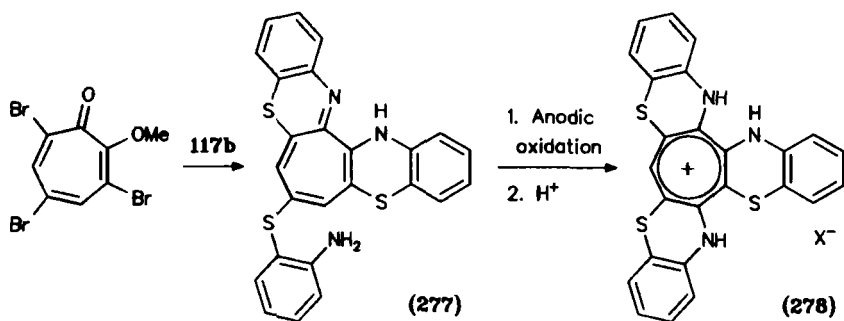
SCHEME 67



SCHEME 68



SCHEME 69



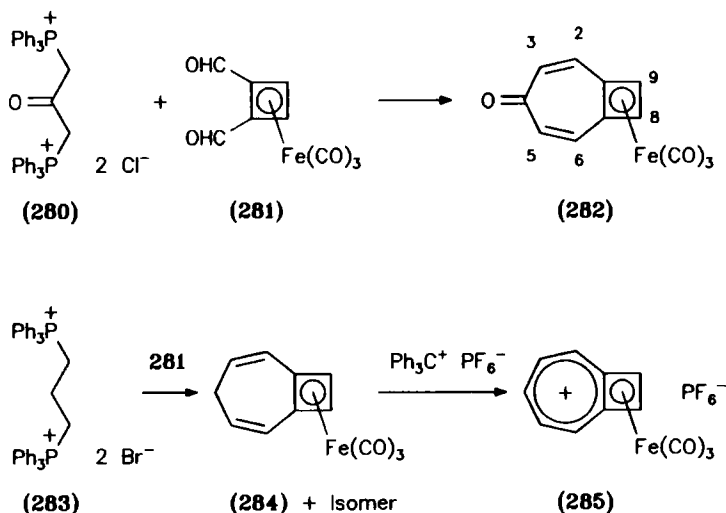
SCHEME 70

- (b) cyclizations involving normal (see **271**, **274**) or cine substitution (Section II,B,1,f),
- (c) nucleophilic addition or substitution by the synthons and subsequent autoxidation (spontaneous dehydrogenation) to produce tropylium systems (e.g., **272**),
- (d) nucleophilic attack by another molecule of synthon resulting in
 - (i) the formation of cycloheptabis(benzazines) (e.g., **268b**),
 - (ii) the intermolecular heterocycle-exchange reaction (see **224c**, **273**), or
 - (iii) the heteroring transposition by the intramolecular migration of the initial synthon (see **276**),
- (e) oxidation or autoxidation of intermediates to produce large polycyclic systems (e.g., **278**).

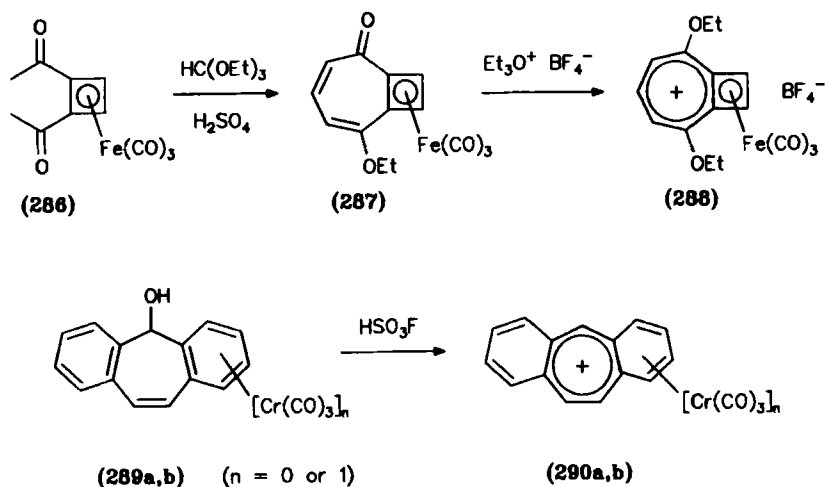
Cycloheptaquinoxaline **222c** with "magic methyl," instead of the expected *N*-methylation, suffers *C*-methylation and *N*-sulfonation to yield betaine **279** (89BCJ1158).

E. SYNTHESSES OF TROPOIDS FUSED TO METAL π -COMPLEXES

(For general syntheses applied to fused ferrocene, tricarbonyl cyclobutadieniron, and benchtrotrene derivatives, see Tables II, IV, V, and VIII.)



SCHEME 71



SCHEME 72

1. Tricarbonyl Cyclobutadiene Iron Derivatives

Annulation of tricarbonyl cyclobutadiene iron to tropone and tropylium ion to give complexes **282** and **285** is achieved by Wittig cycloolefination of dialdehyde **281** with biphosphonium salts, **280** and **283**, respectively (Scheme 71; 77JA513; 78AJC1607).

Furthermore, the homologous complex **286** condenses with ethyl orthoformate to give, in the course of a new γ -tropolone synthesis, tropolone ether **287**; by *O*-ethylation it is transformed to tropylium salt **288** (Scheme 72; 70JA6382); the corresponding tropone complex was synthesized from dibenzotropone and $\text{Cr}(\text{CO})_6$ [83AG(S)734].

2. Tricarbonyl Benzene Chromium Derivatives

Tricyclic complex **290b**⁴ is obtained from its pseudobase **289b** (Scheme 72; 83AG572); the corresponding tropone complex was synthesized from dibenzotropone and $\text{Cr}(\text{CO})_6$ [83AG(S)734].

ACKNOWLEDGMENTS

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⁴ Formula numbers above **290** refer to Part 2.

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⁵ English translations of Russian papers are quoted in the reference section of Part 2.

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Iminophosphoranes: Versatile Tools in Heterocyclic Synthesis

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I. Introduction	160
II. Synthesis of Iminophosphoranes	160
A. The Classical Staudinger Reaction	160
B. The Kirsanov Reaction	164
C. Dihalogenophosphoranes and Primary Amines	165
D. Some Novel Methods	165
III. General Properties	168
A. Structure	168
B. Electron Distribution and Substituent Influence	168
C. Sensitivity to Hydrolysis	170
D. From Polymer-Fixed Triphenylphosphanes to Polymer-Fixed Iminophosphoranes	173
IV. Biological Activity	173
V. Aza-Wittig Reaction	174
A. Mechanism	175
B. Via Aza-Wittig Reaction toward Cyclization	177
C. Reactions with Aldehydes and Ketones	178
D. Reactions with Acid Halides	179
E. Reactions with Heterocumulenes	180
VI. The Aza-Wittig Reaction: A Versatile Principle in Heterocyclic Synthesis . . .	182
A. Three-Membered Heterocycles	182
1. Aziridines	182
2. Oxaziridines	183
B. Four-Membered Heterocycles: Azetidines	184
C. Five-Membered Heterocycles	186
1. Furan and Pyrrole	186
2. Oxazoles and Thiazoles	188
3. Pyrazoles	191
4. Imidazoles	191
5. 1,3,4-Oxadiazoles	194
6. 1,3,4-Thiadiazoles	195
7. 1,2,4-Triazoles	197
8. Tetrazoles	200
D. Six-Membered Heterocycles	202
1. Pyridines	202
2. Quinazolines	204

3. Isoquinolines	206
4. Oxazines and Benzoxazines	208
5. Pyrimidines	212
6. Quinazolines	215
7. Quinoxalines	219
8. Phthalazines	220
9. 1,3,4-Oxadiazines and 1,3,4-Thiadiazines	220
10. 1,2,4-Triazines and 1,3,5-Triazines	221
11. 1,2,4,5-Tetrazines	223
E. Seven-Membered Heterocycles	224
1. Azepines and Derivatives	224
2. Benzazepines	226
3. 1,3-Benzoxazepines	226
4. Benzodiazepines	227
5. Benzotriazepines	228
VII. Iminophosphoranes as Versatile Starting Materials in the Three-Component Reaction: Iminophosphorane–Heterocumulene–Heteroarene	231
A. Heterocondensed Uracil Betaines	231
B. Zwitterionic Heterocyclic Pyrazoles	236
C. Scope and Limitations of the Three-Component Reaction	236
VIII. Conclusion and Outlook	239
References	240

I. Introduction

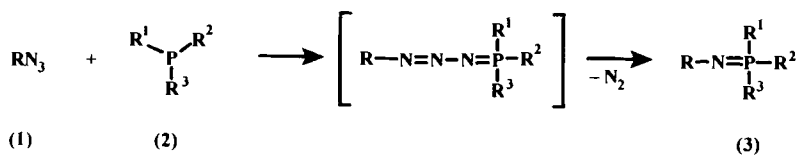
Within the last decades, the aza-Wittig reaction has assumed increasing importance for the specific construction of many heterocyclic systems. This first comprehensive review provides an overview of the synthetic potential exhibited by an iminophosphorane moiety.

Although several recent reviews deal with selected aza-Wittig reactions of iminophosphoranes (91OPP1; 92OPP209, 92T1353; 94S1197), heretofore no detailed synopsis has appeared on the preparative importance of this synthetic principle for individual heterocycles with different ring size.

II. Synthesis of Iminophosphoranes

A. THE CLASSICAL STAUDINGER REACTION

As early as 1919 Staudinger and Meyer reported for the first time the synthesis of an iminophosphorane (**3**) from triphenylphosphane (**2**) and organic azides (**1**) with simultaneous nitrogen extrusion (Scheme 1) (19HCA635). A modern graphic representation of the first Staudinger iminophosphorane is shown in Fig. 1. A facsimile of the original paper published in *Helvetica Chimica Acta* is shown in Fig. 2.



SCHEME 1

Mechanistic studies involving kinetic [55LA117; 67JA5235; 81T437; 87PS(30)393] and X-ray analyses [88AX(C)1080; 89PS149] revealed that nucleophilic attack of the phosphane on the azide occurs with the formation of a *trans*-phosphazide (4) having zwitterionic character [88AX(C)1080; 89PS149], and this reaction is the rate-determining step (55LA117). After *trans* → *cis* isomerization to phosphazide (5), nitrogen is evolved via a four-center intermediate (Scheme 2) (72MI1, 72MI2; 81T437; 92T1353). The rate constant k_1 is decreased by electron-withdrawing substituents at the phosphorus atom, whereas it is increased by the same groups at the azide moiety. The rate of reaction is controlled only inductively [81T437; 87PS(30)393] and k gives direct evidence about the inductive influence of substituents at phosphorus as long as standard conditions are maintained.

All experiments to obtain λ^3 -phosphazenes from chlorophosphanes, phosphane, and phenylphosphane were unsuccessful (19HCA635). Reactivity studies revealed that aliphatic phosphanes react more smoothly than the aromatic ones. However, the azides did not show any differences with respect to their substituents (19HCA635, 19HCA619; 20CB72).

The so-called "Staudinger reaction" is limited only by the availability of the organic azides and their distinct tendency to decompose explosively.

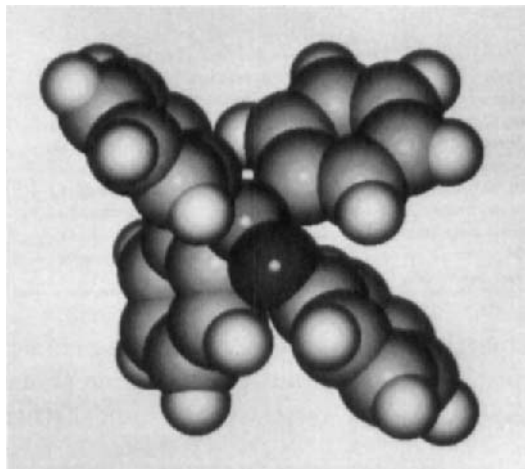


FIG. 1. Graphic representation of the first Staudinger iminophosphorane $\text{PhN}=\text{PPh}_3$ (19HCA635).

HELVETICA CHIMICA ACTA

VOLUMEN II

FASCICULUS PRIMUS

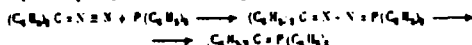
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— 636 —

Über neue organische Phosphorverbindungen III. Phosphinmethylderivate und Phosphinimine

von
H. Staudinger und Jules Meyer.
(10. XI. 19.)

In der vorigen Arbeit wurde gezeigt, dass tertiäre Phosphine und aliphatische Diazoverbindungen sich zu Phosphazinen vereinigen und dass das Triphenylphosphin-Benzophenonazid unter Stickstoffabspaltung in ein Phosphinmethylderivat, das Triphenylphosphin-Diphenylmethylen übergeht.



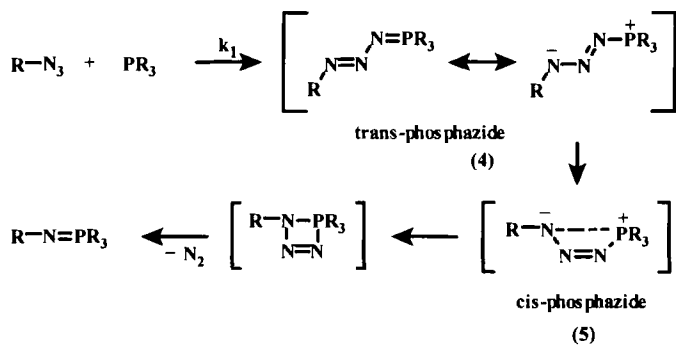
Azide haben ein ähnliches Verhalten wie die aliphatischen Diazoverbindungen und sollten mit den Phosphinen ganz analoge Anlagerungsprodukte, Phosphazide, geben, die unter Stickstoffabspaltung in ein Phosphiniminderivat übergehen sollten.

— 636 —

Phenylazid und Derivate desselben reagieren viel lebhafter mit Phosphinen als das Diphenyldiazomethan. Beim Triäthylphosphin erfolgt fast explosionsartige Umsetzung und auch beim Triphenylphosphin ist es ohne Zugabe von Verdünnungsmitteln sehr lebhaft. Aus Triäthylphosphin und Phenylazid entsteht ein sehr stickstoffreiches Produkt, das vornehmlich ein Phenylazinderivat ist, aber vielleicht eine kompliziertere Zusammensetzung hat. Das Produkt muss noch genauer untersucht werden. Das primäre Anlagerungsprodukt des Triphenylphosphin und Phenylazid ist nicht zu fassen, sondern unter Stickstoffabspaltung erhält man sofort das Triphenylphosphin-Phenylimin.

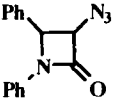
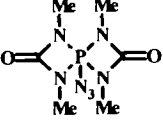
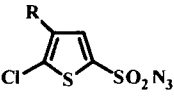
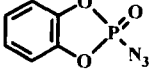
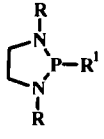
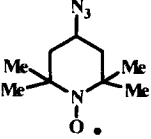
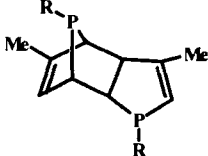
Es ist dies der erste Repräsentant einer neuen und sehr interessanten Körperklasse. Derartige Produkte lassen sich leicht und in fast quantitativer Ausbeute aus verschiedenen aromatischen Aziden (Tolyl-, Xylylazid) und verschiedenen aromatischen Phosphinen gewinnen.

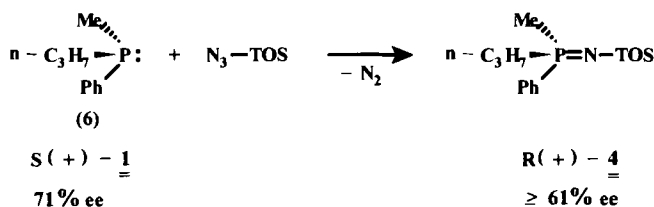
FIG. 2. Facsimile of the original paper on the first iminophosphorane synthesis by Staudinger (19HCA635).



SCHEME 2

 TABLE I
 SOME NOVEL AZIDES AND PHOSPHANES

Azides	References	Phosphanes	References
	82ZOB2797	$\text{R}_2\text{N}-\text{PF}_2$	84ZC138
	86PS193 87CB1713	$(\text{EtO})_2\text{P}-\text{O}-\overset{\text{R}}{\underset{ }{\text{C}}}=\text{CR}_2^1$	83ZOB1022
	82PS119	$(\text{EtO})_2\text{P}-\text{X}-\text{P}(\text{OEt})_2$ $\text{X} = \text{NPh or CH}_2$	83ZOB656 82UKZ386
	83ZOB285 87ZOB1967		81PS11
	82S147		87PS(31)133



SCHEME 3

Some novel azides and phosphanes are depicted in Table I.

If chiral phosphanes (6) are employed, retention of configuration is observed (Scheme 3) (81TL3827).

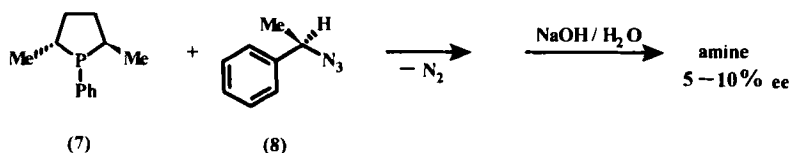
Wilson and Pasternak reported the first asymmetric Staudinger reaction (Scheme 4) where the chiral phosphane (7) reacts with the racemic azide (8) to afford diastereomeric iminophosphoranes in different quantities, giving after hydrolysis an amine in slight enantiomeric excess. Separation of the racemate seems to be kinetically controlled, but needs optimization (90MI1).

B. THE KIRSANOV REACTION

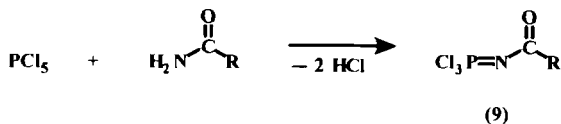
The Kirsanov reaction (Scheme 5) is a valuable supplement to the Staudinger reaction; starting from phosphorus pentachloride and amine or amide derivatives it opens an access to *P*-halogenated iminophosphorane 9 (50IZV426).

A variant of the Kirsanov reaction was developed by Zimmer *et al.*, where the system iodine/base/triphenylphosphane was used for the preparation of iminophosphoranes (68TL3811).

The *P*-halogenated iminophosphoranes can be subsequently transformed into trialkyl-, triaryl-, and trialkoxyiminophosphoranes by nucleophilic substitution [56ZOB903, 56ZOB907; 66MI1; 75JCS(D)2527; 89MI1].



SCHEME 4



SCHEME 5

C. DIHALOGENOPHOSPHORANES AND PRIMARY AMINES

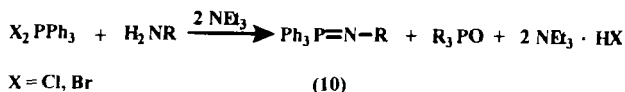
Since many functional groups react with phosphorus pentachloride, the synthesis of iminophosphoranes (**10**) from dihalogenophosphoranes and primary amines (Scheme 6) represents one of the most versatile routes to this class of compounds (59LA142; 66MI1).

The elusive dihalogenophosphoranes can be obtained directly from trivalent phosphorus compounds and elementary halogen (59LA142). A new and excellent preparation of dichlorotriphenylphosphorane prevents the generation of undesirable phosphorus and chlorocarbon by-products. Thus, 0.3 equivalent of triphosgene was added to a solution of triphenylphosphane (in CH_2Cl_2 , CHCl_3 , or MeCN), resulting in the quantitative formation of dichlorotriphenylphosphorane (94SC1715).

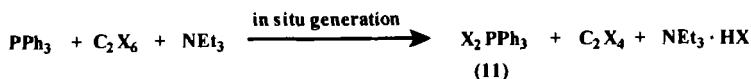
Appel improved this preparation by the development of an elegant and direct *in situ* procedure starting from triphenylphosphane (Scheme 7). This method produces highly reactive dihalogenotriphenylphosphorane **11** (70CB3631; 75AG863; 77CB2382, 77CB3209; 79MI1), and has been extended to the easy preparation of dibromotriphenylphosphorane (83S139). The fast and smooth Appel procedure has found broad application, especially for the easy preparation of iminophosphoranes of heterocyclic β -enamino esters.

D. SOME NOVEL METHODS

A recent communication is based on the nucleophilic substitution of *N*-silylated iminophosphoranes (Scheme 8), where activated chloro- (**12**) and nitro heterocycles (**13**) (triazines, pyrazines, and pyridines) are transformed into monosubstituted iminophosphoranes (**14**). Of special advantage are the mild reaction conditions and the preferential formation of monosubstituted



SCHEME 6

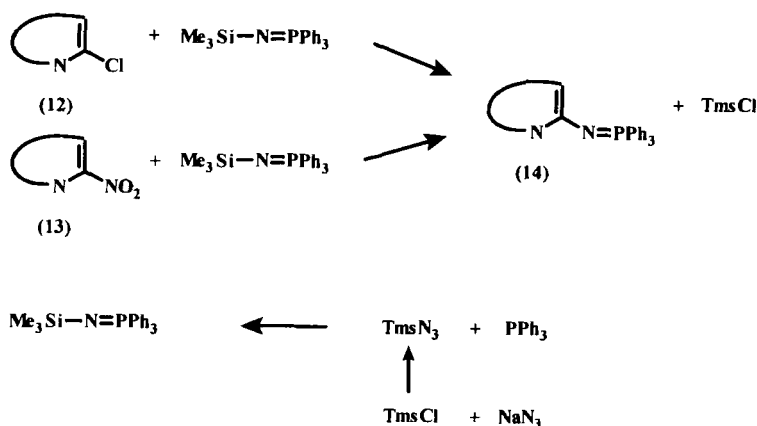


SCHEME 7

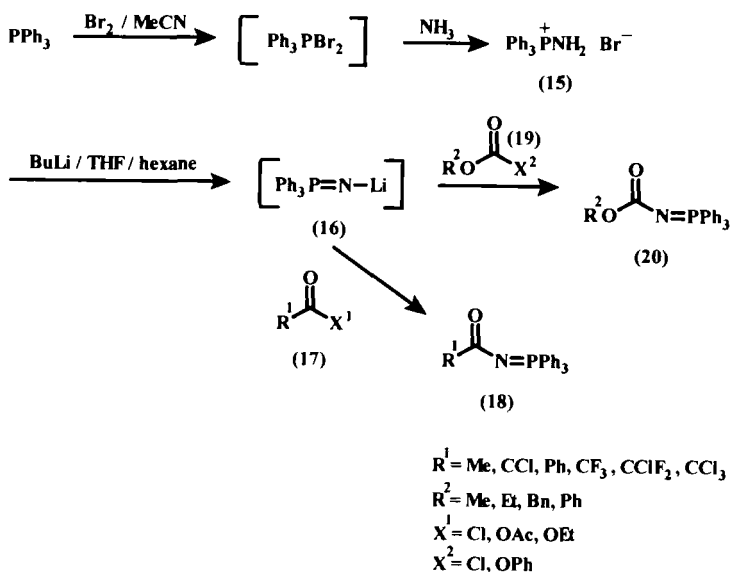
iminophosphoranes, even when polyfunctional heterocycles are employed (63CB2751; 93PS309).

Acyliminophosphoranes are easily accessible from lithiated triphenyliminophosphoranes (**16**), the latter being generated by lithiation of phosphonium bromides (Scheme 9). The strongly basic iminophosphorane anion reacts either with an acyl halide (**17**) or a chlorocarbonate (**19**) to give triphenyl-*N*-acyliminophosphorane (**18**) or product (**20**), respectively (91S382).

N-Vinyliminophosphoranes were hitherto accessible only from the explosive vinyl azides and trialkyl or triarylphosphanes. However, E. Ciganek developed a new route to vinyl iminophosphoranes via addition of resonance-stabilized ylides e.g., α -(triphenylphosphoranylidene)toluene to activated nitriles, cyanogen, or trifluoroacetonitrile. The mechanism involves formation of an adduct followed by ring closure to the dihydrophosphazete. The desired vinyl iminophosphorane results by opening of the four-membered ring (70JOC3631). Moreover by Katritzky's benzotriazole method (Scheme 10), azidoalkylbenzotriazole **21** can be converted accord-

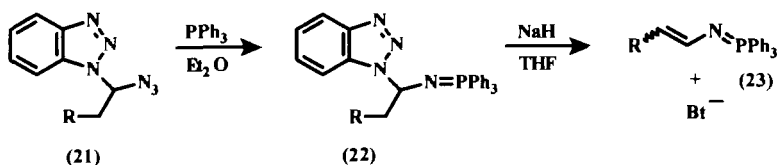


SCHEME 8

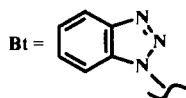


SCHEME 9

ing to Staudinger's conditions into the appropriate iminophosphorane (**22**) containing a proton β to nitrogen (94JOC2740). Treatment with NaH gives vinyliminophosphorane (**23**) in a mixture of *Z/E* isomers, predominantly the *Z*-isomer. The *Z:E*-ratio depends on the nature of the β -substituent ($\text{Me} = 85:15$, $\text{Ph} = 57:43$) (94JOC2740).



$\text{R} = \text{H}, \text{Me}, \text{Et}, \text{Ph}, i\text{-Pr}$



SCHEME 10

III. General Properties

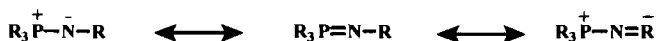
A. STRUCTURE

The structural formula of iminophosphoranes is usually depicted as having a double bond. However, the correct bonding situation is described in terms of several additional dipolar canonical formulas, as shown in Scheme 11 (66MI1; 72MI1; 74CSR87; 85JOC1757; 86JOC1223).

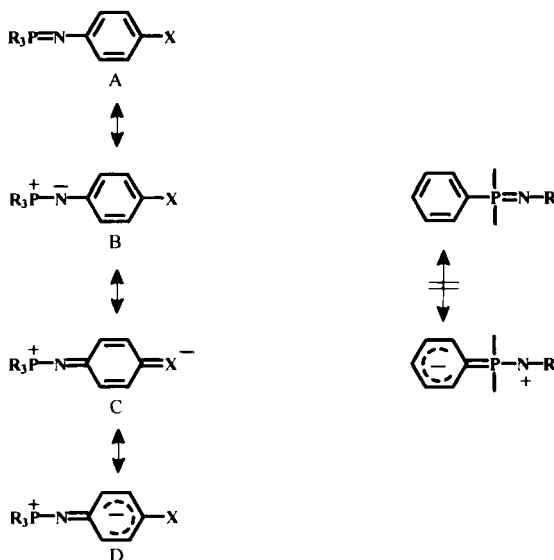
Spectroscopic investigations [59LA142; 74AX(B)221; 75PAC343; 79IC3307; 85JOC1757; 86AX(B)462, 86JOC1223, 86PS175; 87JOC159, 87PS(30)799; 91JOC2762], dipole measurements (74BSF819, 74MI1), and X-ray analyses [74AX(B)221; 86AX(B)462, 86PS175] reveal that the bond lengths of iminophosphoranes correspond to a P=N double bond with significant $p\pi$ - $d\pi$ -character. The tetrahedral phosphorus exists as an sp^3 -hybrid, and the nitrogen as an sp^2 -hybrid. Depending on the nature of the substituent, the amount of double-bond character can vary. This is shown by the variable dipole moment and the broad frequency range of the P—N stretching vibration between $\nu = 1141$ – 1500 cm^{-1} . Thus, the bonding order at the N atom is increased by electron-withdrawing groups, and the partial positive charge at the P atom is strengthened. This leads to a contraction of the d -orbitals, which enables a better overlap with the p -orbitals at the N atom (72MI1, 72MI2; 74CSR87).

B. ELECTRON DISTRIBUTION AND SUBSTITUENT INFLUENCE

Delocalization of the partial charge at the N atom is also found on *N*-aryl-substituted iminophosphoranes, where conjugation with the aromatic ring requires a consideration of additional resonance formulas (72MI1, 72MI2; 74CSR87; 85JOC1757; 86JOC1223). In this regard, heteroaromatic substituents or electron-withdrawing substituents in an *o*- and *p*-position lead to good stabilization (85JPR327). However, conjugation with aryl substituents at the P atom is not favorable (72MI1, 72MI2; 74CSR87), as shown in Scheme 12. ^{15}N - and ^{31}P -NMR shifts are sensitive toward changes in the amount of resonance forms **B** and **D** which do not correlate with the amount of $p\pi$ - $d\pi$ -interaction (85JOC1757), since $p\pi$ - σ^* -overlaps also play a role (86JOC1223).



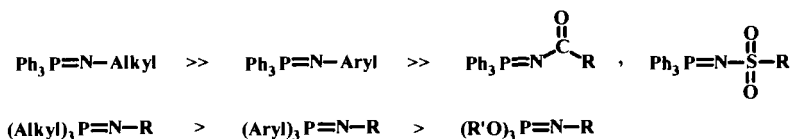
SCHEME 11



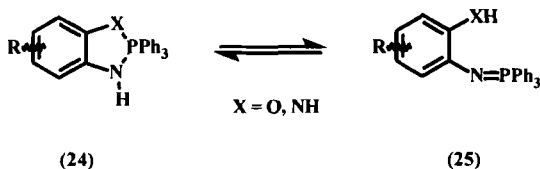
SCHEME 12

It is generally observed that the stability, basicity, and nucleophilicity of iminophosphoranes are mainly determined by the substituents on the nitrogen atom (21HCA861, 21HCA887; 55LA117; 66MI1), as indicated in Scheme 13. The phosphorus atom hampers the transmission of substituent effects within the molecule, and only strongly electron-withdrawing *P*-ligands, such as alkoxy groups, can prevent a reaction [67JCS(C)2018]. The higher reactivity of *P*-alkyl iminophosphoranes can be explained by steric effects (21HCA861).

An equilibrium between iminophosphorane **25** and 1,3,2-benzoxaphosphole **24** or 1,3,2-benzodiazophosphole (Scheme 14) is established if an ortho amino or hydroxy function is adjacent to the $P=N$ double bond. The position of this equilibrium shows solvent dependence [77CB3817; 88CB1685; 90PS(48)223]. In the solid state, only the phosphole form exists, but in polar solvents the iminophosphorane predominates (88CB1685).



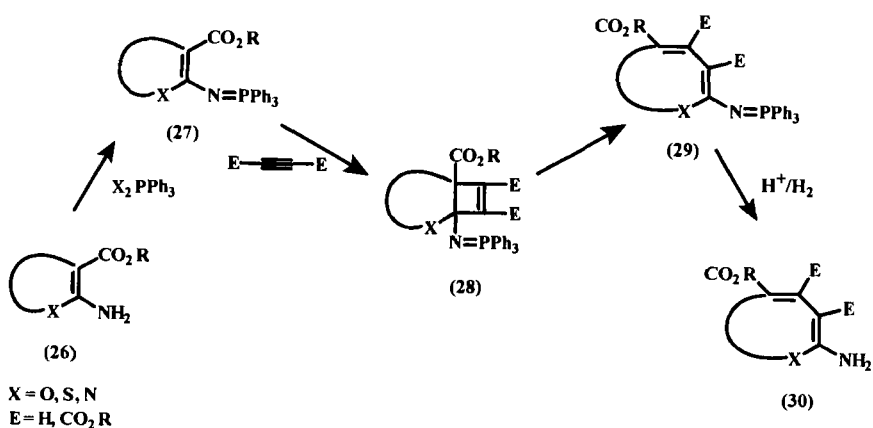
SCHEME 13



SCHEME 14

C. SENSITIVITY TO HYDROLYSIS

Because of its sensitivity toward hydrolysis, the iminophosphorane moiety is an attractive protecting group. Thus, Wamhoff *et al.* have employed iminophosphorane groups in a broad range of heterocyclic β -enamino esters, which are key compounds for constructing many new heterocyclic systems (76CB1269; 81CB3188; 83CB1691; 84CB585; 85AHC299, 85 LA1910; 86CB3515; 88CB2157, 88S919). Reactions with electrophiles require protection of the amino function within enamino esters when strong competition for the nucleophilic centers exists. (For examples, see Section VI.) Wamhoff *et al.* developed the cycloaddition–ring-enlargement (CARE) sequence (Scheme 15) employing iminophosphoranes (**27**) as an amino protecting group for β -enamino esters (**26**) and enamino nitriles. The five- or six-membered heterocyclic iminophosphoranes cyclize to an intermediate cyclobutene adduct (**28**), which spontaneously undergoes ring



SCHEME 15

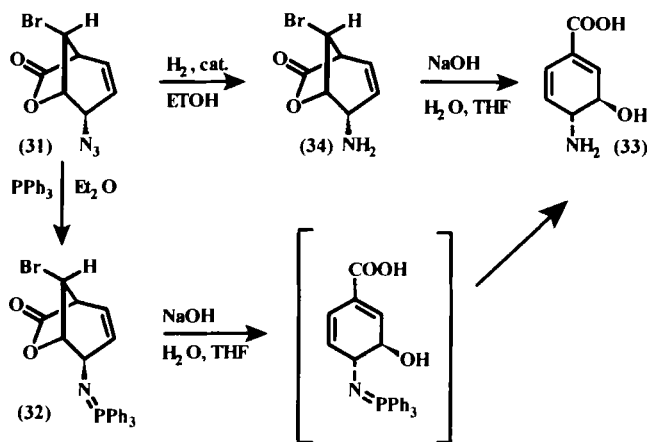
enlargement *in situ* to give seven- or eight-membered heterocycles (**29**). Deprotection by acid hydrolysis then results in the ring-enlarged enamino ester (**30**) with a free amino group (85AHC299).

Alternatively organic azides can easily be transformed into primary amines via a Staudinger reaction and subsequent hydrogenolysis (19HCA635; 21HCA861; 81T437; 91OPP1).

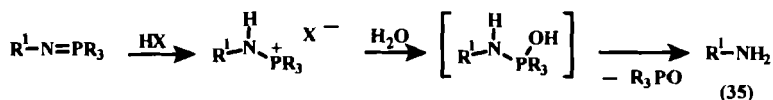
Employing iminophosphoranes to protect a group labile under alkaline conditions can lead to a dramatic increase in yield. This is exemplified by the transformation of allylic azide **31** into the corresponding iminophosphorane **32** shown in Scheme 16. Hydrolysis under basic conditions leads finally to 4-amino-3-hydroxycyclohexa-1,5-diene-1-carboxylic acid (**33**) in 80% yield. However, when the same azide (**31**) is converted with a Lindlar catalyst, via allylic amine **34** into carboxylic acid **33**, only 0–30% yields are found as a consequence of the low stability of the allylic amine [93JCR(S)148].

Some time ago Staudinger investigated the tendency to hydrolysis of iminophosphoranes; like the reactivity, hydrolysis is strongly dependent on the nature of the *N*-substituent. The hydrolysis of iminophosphoranes by acids is initiated by a protonation step on the nitrogen to form an amine (**35**), as shown in Scheme 17.

In the course of these reactions, the appropriate aminophosphonium salt can be isolated by employing anhydrous acids and *N*-alkyliminophosphoranes (21HCA861; 55LA117; 72PS35). In the case of aryliminophosphoranes, these phosphonium salts can be obtained even with dilute acids [55LA117; 59LA142; 72PS35; 88JCS(P1)2329]. By reaction with H_2O , this cation is



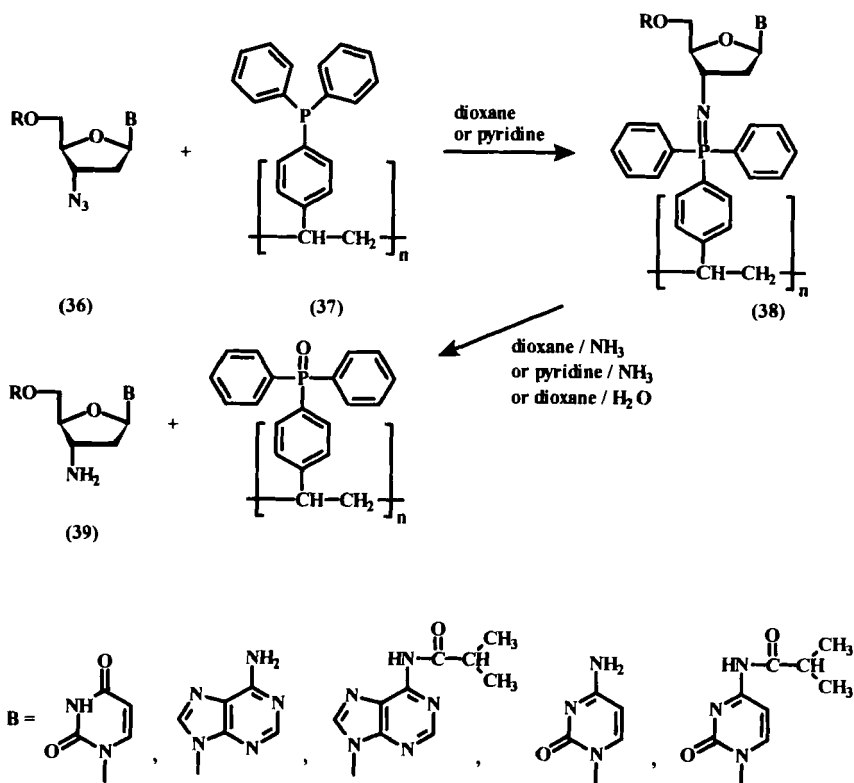
SCHEME 16



SCHEME 17

converted into an intermediate with pentacoordinated phosphorus, the latter decomposing into a primary amine and a phosphane oxide.

Upon basic hydrolysis, the OH^- is added to the $\text{P}=\text{N}$ double bond and the protonation step follows [89JOC3292, 89TL3303; 90PS(49/50)151, 90S398, 90T2149].



R = H, DMTr (4,4'-dimethoxytrityl)

SCHEME 18

D. FROM POLYMER-FIXED TRIPHENYLPHOSPHANES TO POLYMER-FIXED IMINOPHOSPHORANES

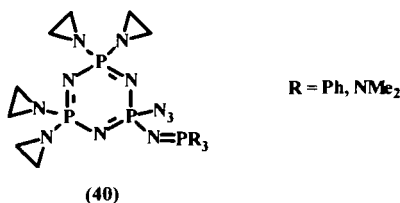
Because triphenylphosphane can be attached to a polymer carrier, this technique is used in the transformation of azido nucleosides into amino nucleosides. When the conventional method—i.e., treatment of the azide with triphenylphosphane and subsequent hydrolysis of the resulting iminophosphorane—is used, separation of the triphenylphosphane oxide can be difficult. Using polymer-fixed triphenylphosphane, e.g., the commercially available polystyryl diphenylphosphane resin, has been successful in the aza-Wittig reaction (83JOC326), in the acetalization of carbonyl compounds (87S386), and in the transformation of alcohols into alkyl chlorides (86S499). The advantage of this novel method (94S789) consists in the easy isolation of the reaction product in high yield (89–100%). The polymer-fixed triphenylphosphane oxide can be removed by simple filtration (cf. Scheme 18) (94S789).

As shown in Scheme 18, the reaction of 3-azido-2,3-dideoxynucleoside **36** with polystyryl diphenylphosphane resin (**37**) affords iminophosphorane **38**, which gives amine **39** after hydrolysis. Dioxane or pyridine is used as a solvent, and the purity of the products obtained is identical with those obtained by the normal method (94S789).

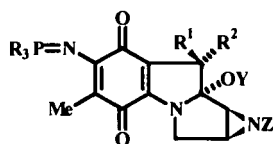
IV. Biological Activity

So far, not much literature on the biological activity of iminophosphoranes has appeared. Compounds possessing triorganylphosphoranylideneamino structural elements such as mitomycin (**41**) have proved to be interesting anti-tumor reagents; the cancerostatic activity seems to be localized in the aziridine units of **40** (Scheme 19) [87PS(30)845].

Additional anti-tumor agents exhibiting antibacterial activity are the iminophosphorane derivatives of mitomycin (**41**), with phenyl-, alkyl-, or



SCHEME 19



(41)

Y, Z = H, Me

R¹, R² = methylene

R = alkyl, cycloalkyl, phenyl

SCHEME 20

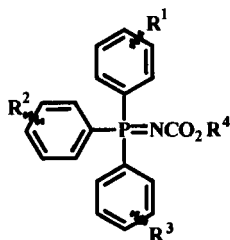
cycloalkyl substituents on the phosphorus (Scheme 20) [88JAP(K)63/54, 380].

Similar activities have been found on *N*-alkyl-*N*-2,2-dimethylvinyliminophosphate (88MI1). *N*-Carbonyltriaryliminophosphoranes (**42**; Scheme 21), which have been employed as diuretics, have been shown to decrease plasma-renine activity (88USP4767749).

Recently, the potential of organometallic iminophosphoranes as synthetic components for radiopharmaceutical agents has been reported. In nuclear medicine ¹⁸⁸Rh is currently being used as a radioisotope for diagnostics and cancer therapy. A complex of ¹⁸⁸Rh with organometallic iminophosphoranes, such as **43** (Scheme 22), could represent a novel type of radiopharmaceutical [93ZN(B)1381].

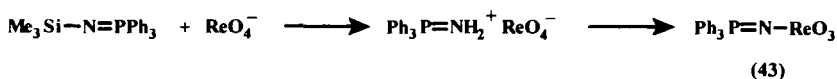
V. Aza-Wittig Reaction

Staudinger *et al.* (19HCA635; 20CB72; 21HCA861, 21HCA887) investigated this important reaction type for several carbonyl compounds and heteroanalog systems with respect to its scope and limitations. Currently, the aza-Wittig reaction (named in analogy to the Wittig reaction) has become one of the most important synthetic methods for constructing



(42)

SCHEME 21



SCHEME 22

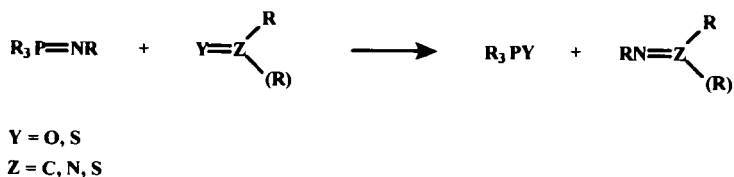
novel $-\text{C}=\text{N}-$, $-\text{N}=\text{N}-$, and $-\text{S}=\text{N}-$ bonds, especially in modern heterocyclic synthesis. The general reaction type is depicted in Scheme 23 (67MI1).

A. MECHANISM

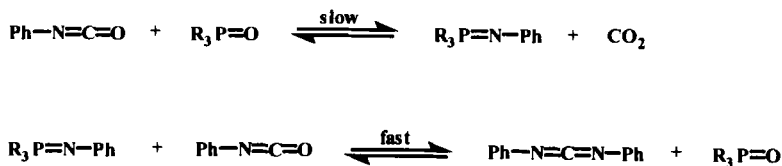
The first publications to describe the phosphane oxide-catalyzed carbodiimide synthesis from isocyanate appeared in 1962. In this case iminophosphoranes were recognized as important intermediates. The first mechanistic studies also appeared at this time. Scheme 24 depicts the proposed two-step mechanism (62JA3673, 62JA4288; 66CJC2793).

The rate-determining first step is the reaction of the isocyanate with phosphane oxide, resulting in the formation of isocyanate and CO_2 . Once the isocyanate is formed, it reacts with additional isocyanate to give carbodiimide and regenerate the catalyst. A more detailed investigation of the reaction mechanism (Scheme 25) followed years later (69ACSA2697; 72ACSA1777).

For the reaction of phosphane oxide with isocyanate, the rate-determining step is the formation of the oxazaphosphetane **45** via $\text{P}-\text{O}$ -bond formation of the intermediate betaine (**44**), since the stable and energetically favorable $\text{P}=\text{O}$ double bond is broken here. Subsequent rapid decomposition of the oxazaphosphetane **45** into iminophosphorane and carbon dioxide occurs. Within the actual aza-Wittig step, the intermediate betaine (**46**) is generated in a rate-determining step by nucleophilic attack of the iminophosphorane nitrogen on the carbonyl C. By $\text{P}-\text{O}$ -bond formation, betaine (**46**) is then converted into an oxazaphosphetane (**47**), which decomposes



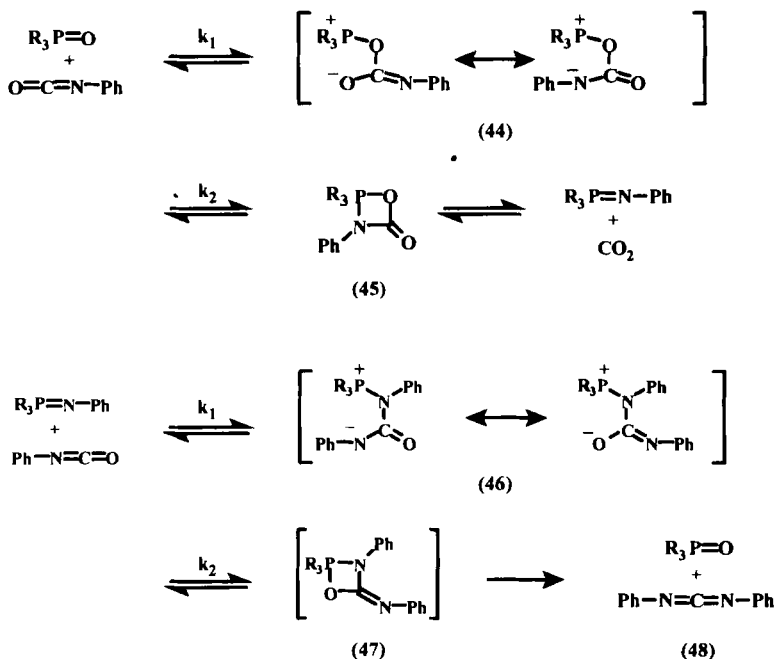
SCHEME 23



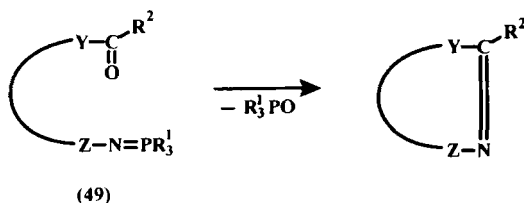
SCHEME 24

into phosphane oxide and carbodiimide (**48**). The driving force for this reaction is the rapid formation of the stable, low-energy phosphane oxide (62JA4288; 69ACS2967). Investigations have shown that these reactions proceed faster in polar protic solvents than in nonpolar or dipolar aprotic solvents (66CJC2793; 72ACS1777).

Unlike phosphane oxide, the reaction rates of the iminophosphoranes exhibit no dependence on the P substituents. The initial step is a factor of 10^5 – 10^7 slower than the second step. However, the nucleophilicity of the iminophosphoranes can influence the reaction rate; thus, electron-donating



SCHEME 25



SCHEME 26

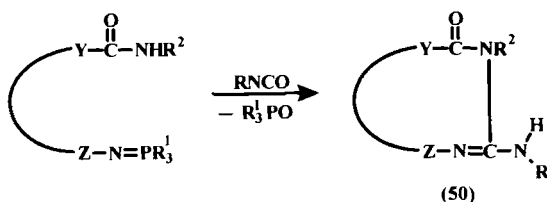
substituents on the *N*-phenyl group increase the electron density and hence the nucleophilicity of the N atom, so that k_1 is decreased. (66CJC2793; 72JOC1850). Phospholes possess the best catalytic properties (phosphole effect), but phosphates, sulfoxides, and arsenic oxides are also suitable catalysts (62JOC3851; 66MI1).

B. VIA AZA-WITTIG REACTION TOWARD CYCLIZATION

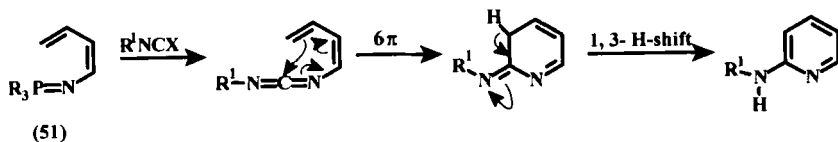
The aza-Wittig reaction offers several strategies for the syntheses of heterocyclic compounds, and in Section VI a broad choice of examples is presented. Aza-Wittig reactions can be divided into an *intramolecular* and an *intermolecular* variant, the former starting with a molecule **49** (Scheme 26) that contains both an iminophosphorane group and a carbonyl function in a geometrically favorable orientation.

In the case of the intermolecular variant, the iminophosphorane reacts with an added heterocumulene component to give a carbodiimide **50** (Scheme 27), thus forming a new electrophilic center within the molecule, which can be intramolecularly intercepted by another nucleophilic site of the intermediate.

Conjugated heterocumulenes generated *in situ* by an aza-Wittig reaction are also capable of electrocyclic-ring closure with a subsequent 1,3-H shift. This principle, applied for the first time by Saito *et al.* on butadiene iminophosphorane **51** (Scheme 28) by treatment with isocyanate and isothiocya-



SCHEME 27



SCHEME 28

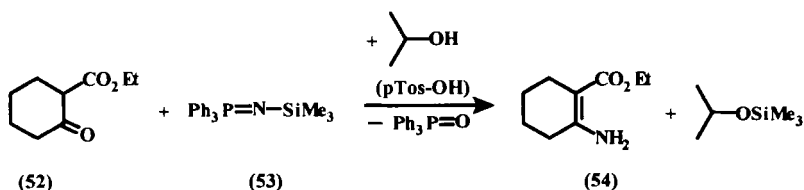
nate (86CL135), was later broadly applied by Molina's group for heterocyclization reactions called tandem aza-Wittig/ 6π -electrocyclizations (94S1197); cf. Section VI.

C. REACTIONS WITH ALDEHYDES AND KETONES

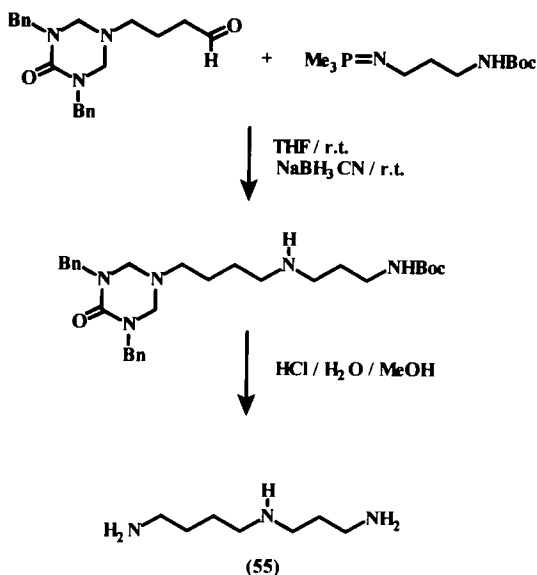
Use of the aza-Wittig reaction with aldehydes (67CB1120) and ketones (72CB1209) leads to several interesting classes of compounds. By this method, β -diketones or β -keto esters (**52**) react with iminophosphorane **53**, which can be transformed *in situ* into the corresponding enamines **54** (Scheme 29). Carbocyclic β -enamino esters can easily be obtained by this procedure (78JOC1460; 90LA995; 93S1129).

Vinyliminophosphoranes are converted by aldehydes into 2-aza-1,3-dienes, which are versatile reagents for cycloadditions (88TL4863). In the presence of triphenylphosphane, azides can be directly transformed with aldehydes or ketones into imines without isolation of the iminophosphorane intermediates (84JOC2688; 88TL6651; 89JOC3292). Imines obtained via an aza-Wittig reaction can be directly reduced to amines, with sodium borohydride or sodium cyanoborohydride serving as reducing agents. This one-pot procedure is used in the synthesis of polyamines (88TL6651) and spermine **55** (Scheme 30) (88TL6651; 90TL2109).

The reaction of *N*-aminotriphenyliminophosphoranes with aldehydes and ketones is influenced by the presence or absence of water: under anhydrous conditions phosphazines (65TL1447) are formed, while trace amounts of water lead to the formation of hydrazones (64AG991) and phosphane oxide.



SCHEME 29



SCHEME 30

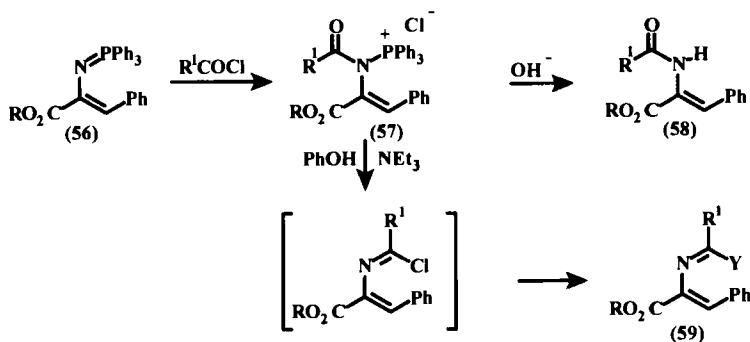
D. REACTIONS WITH ACID HALIDES

Since the electrophilic character of carbonyl groups in acid halides is more pronounced than in carboxylic anhydrides, the former are better suited for aza-Wittig reactions. Zbiral *et al.* studied the reaction of iminophosphoranes with acid halides and obtained imidoyl halides (69LA29; 72PS35). *N*-alkyl and *N*-aryl iminophosphoranes can be set to use in this reaction (72PS35).

Acid halides react with vinylphosphoranes (**56**) to afford isolable *N*-acylaminophosphonium salts (**57**), which are hydrolyzed by alkali to *N*-vinylamides (**58**). By treatment with triethylamine and phenol the halogen in **57** can be nucleophilically exchanged for phenolate. Thiophenol, secondary amines, and hydrazones can be employed instead of phenol; this leads to diverse 1-hetero-substituted 2-aza-1,3-dienes **59** (Scheme 31) (90TL3497).

The smooth hydrolysis of imidoyl chlorides provides access to carbonamides from iminophosphoranes via an aza-Wittig reaction, without the occurrence of free acid or amino functions. This is of special advantage in the synthesis (Scheme 32) of sensitive substrates such as β -lactam antibiotics (**60**) (77H719, 79JOC4393).

Additional investigations have concentrated on reactions of acetyl bromide and iminophosphoranes. The intermediate imide bromide can only be



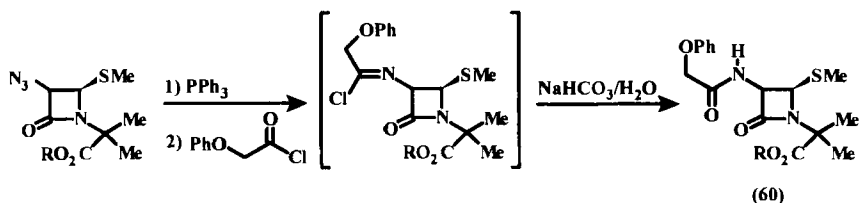
SCHEME 31

isolated as a trapped product, while the latter react with base or nucleophilic iminophosphorane to give amidino- and aminophosphonium salts, respectively (67JA6287; 90JMC845; 91JMC1426). Acid iodides can be employed only if they contain aromatic substituents (72PS35). For the annulation of oxazines by treatment of iminophosphoranes with acid halides, see Section VI.D.4.

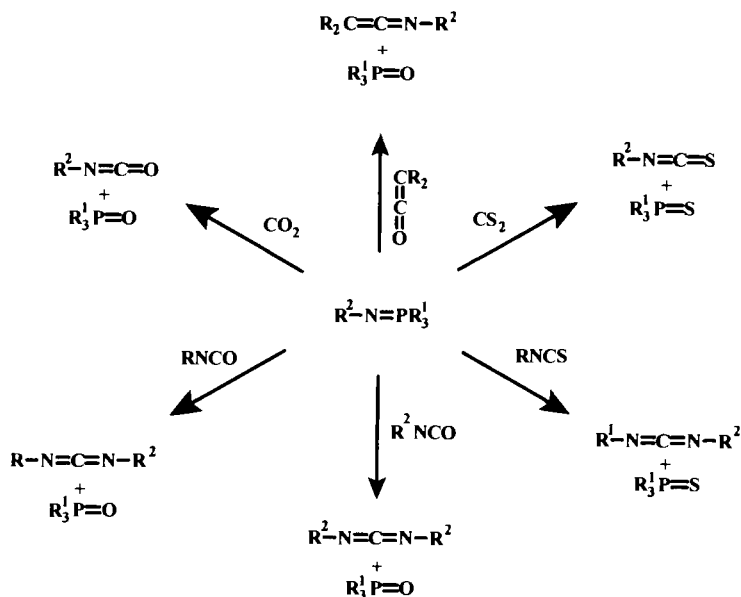
E. REACTIONS WITH HETEROCUMULENES

Owing to their high electron deficiency, heterocumulenes belong to the most reactive class of carbonyl and heterocarbonyl compounds (19HCA619, 19HCA635; 20CB72; 21HCA861, 21HCA887), which makes them especially suited for aza-Wittig reactions. Scheme 33 depicts the synthetic potential of heterocumulenes and iminophosphoranes for aza-Wittig reactions.

Reactivity studies on the iminophosphoranes have revealed that *N*-alkyl derivatives show a higher reactivity than *N*-aryl or *N*-vinyl derivatives. The order of reactivity of the heterocumulenes shown in Scheme 33 is given in Scheme 34 (21HCA861).



SCHEME 32



SCHEME 33

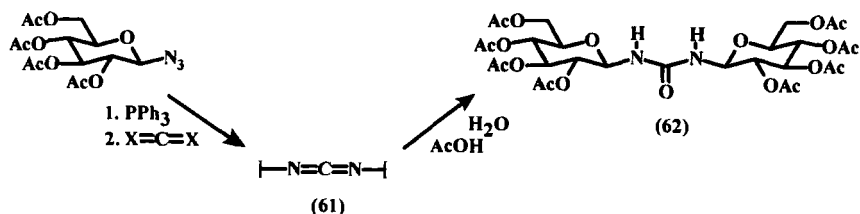
Because of their many side reactions, sulfonyl isocyanates, and especially the highly reactive chlorosulfonyl isocyanates, have been only sporadically employed (21HCA861).

A very special example is shown in Scheme 35 with the formation of bisglucosylcarbodiimides (**61**) from 2-azidoglucose via an aza-Wittig reaction with CO_2 or CS_2 . Subsequent addition of water affords bisglucosyl ureas (**62**) (64AG227). Further examples for the syntheses of carbodiimides are presented in Section VI.

Ketenes, which are even more reactive than isocyanates, afford ketenimines at or below room temperature [62CRV247; 84JOC2688; 89JCS(P1)2140]. At elevated temperatures, dimerization or polymerization occurs (21HCA887). Although *N*-aryl- and *N*-vinyliminophosphoranes react smoothly with ketenes, strong acceptor substituents on the nitrogen hamper the reaction; thus *N*-acyliminophosphoranes do not react with ketenes. Vinylketenimines such as 2-aza-1,3-dienes prepared in this way from



SCHEME 34



SCHEME 35

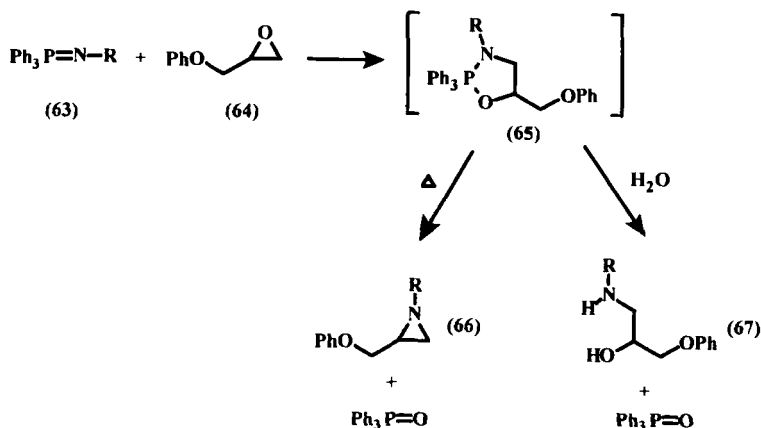
vinyliminophosphoranes are valuable $[4 + 2]$ -cycloaddition partners (62 CRV247).

VI. The Aza-Wittig Reaction: A Versatile Principle in Heterocyclic Synthesis

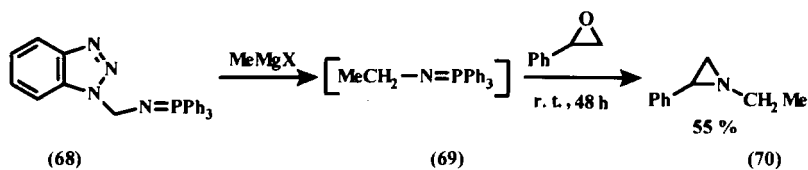
A. THREE-MEMBERED HETEROCYCLES

1. Aziridines

The methods described here use oxiranes as reaction partners of iminophosphoranes. The analogous electrophilicity of the oxiranes and the rather similar mechanism of an aza-Wittig-variant, however, justify their description within this section. Reaction of iminophosphorane **63** with phenoxymethyloxirane **64** (Scheme 36) leads at low temperature to 1,3,2-



SCHEME 36



SCHEME 37

oxaphospholidine **65**, which is either converted by thermolytic phosphane oxide extrusion to give the corresponding aziridine **66** or hydrolyzed by addition of water to aminoethanol **67** (76CB814).

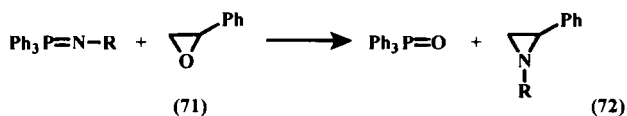
Aziridines are obtained in a novel one-pot synthesis (Scheme 37) by reacting 1-(triphenylphosphoranylideneamino)benzotriazole (BETMIP) **68** with Grignard reagents. The resulting aliphatic *N*-substituted iminophosphoranes (**69**) are converted *in situ* with oxiranes to give aziridines (**70**) (90S565).

Appel *et al.* (76CB814) have treated oxiranes (**71**) with *N*-substituted iminophosphoranes leading to the aziridines (**72**) (Scheme 38).

In another approach, 2-(alkylamino)alcohol is employed as starting material for aziridine syntheses with the aid of dihalogenophosphoranes (70BCJ1185). Intramolecular transformation of 3-azidopropylloxirane **73** results in a simultaneous formation of a condensed aziridino[1,2-*a*]pyrrolidine system (Scheme 39). The azide group is first transformed into iminophosphorane **74**, the nucleophilic N atom cleaves the oxirane to form betaine **75** [as in the Mitsunobu reaction (81S1)], and the phosphorus is shifted from N to O and then eliminated as phosphane oxide under simultaneous cyclization to bicyclic **76** (89JA7500).

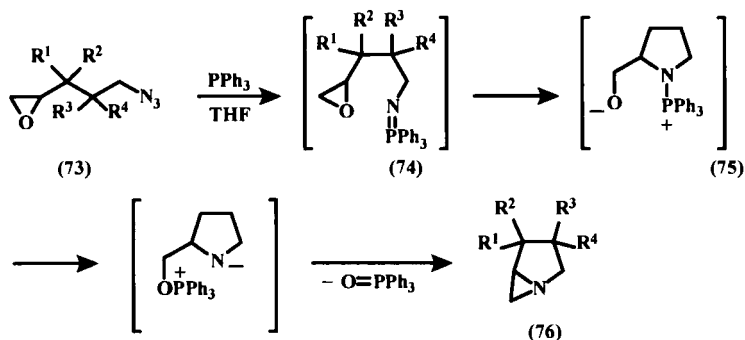
2. Oxaziridines

Oxaziridines (**80**) are obtained by an aza-Wittig reaction of benzaldehyde **77** and *N*-Boc-triphenyliminophosphorane **78** and subsequent ozonolysis of the imine **79**, as shown in Scheme 40 (93JOC4791).



R = Me, Et, *i*-Pr, Ph

SCHEME 38

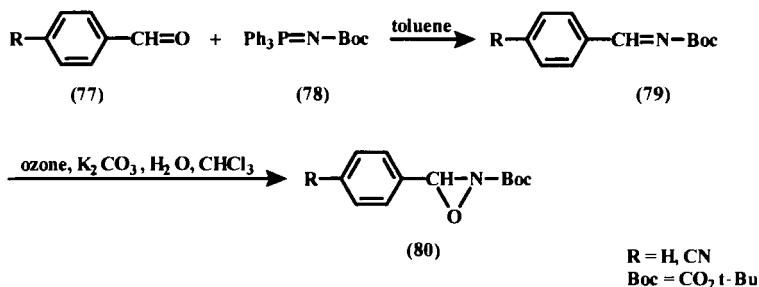


SCHEME 39

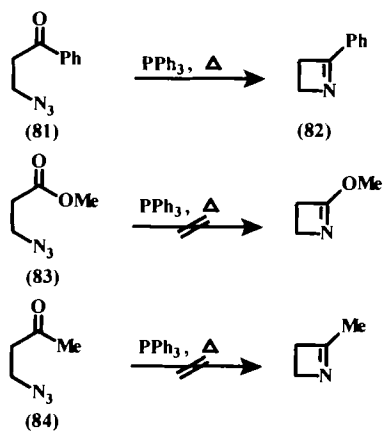
B. FOUR-MEMBERED HETEROCYCLES: AZETIDINES

The only example known for the formation of azetidine **82** by direct intramolecular aza-Wittig reaction is the reaction of the β -azidoketone **81** with triphenylphosphane (Scheme 41). Attempts to transfer this reaction to **83** and **84** were not successful (87NKK1250). This failure can be attributed to the formation of intermediates with highly energetic transition states, where the rate of intramolecular attack on the carbonyl function is so slow that oligo- and polymeric compounds are preferentially formed.

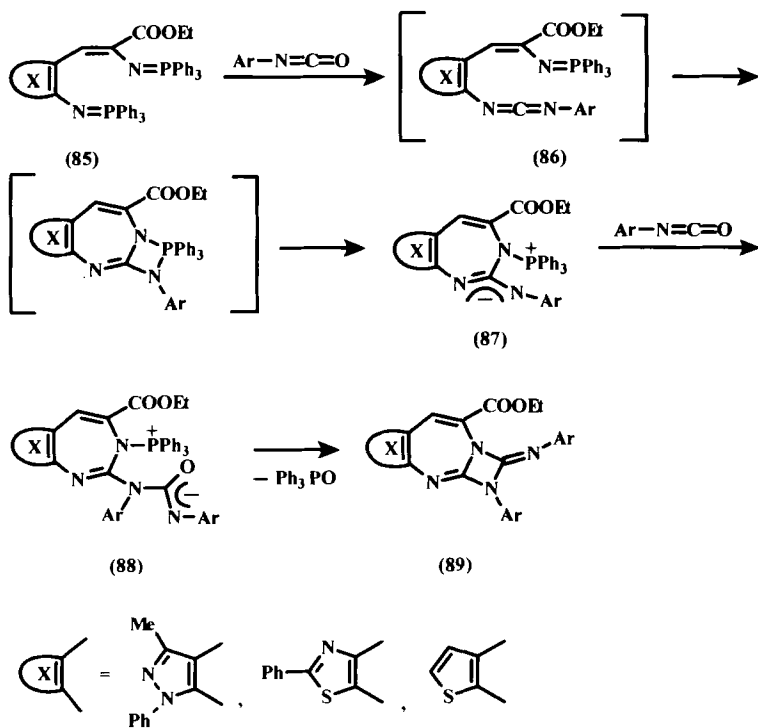
A recent review on four-membered heterocycles formed from iminophosphoranes concentrates on the preparation and the reactivity of 2,4-diimino-1,3-diazetidines and related compounds (93JPR305). As an example, the synthesis via bisiminophosphorane **85** is described in Scheme 42. The bisiminophosphorane has both a heteroaryl and a styryl site. From a mechanistic view, the reaction of the bisiminophosphorane proceeds with aryl isocyanate formation via an aza-Wittig mechanism. Intermediate carbodiimide formation (**86**) occurs directly on the iminophosphorane moiety



SCHEME 40

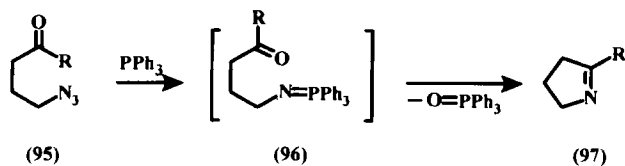


SCHEME 41



SCHEME 42

SCHEME 43

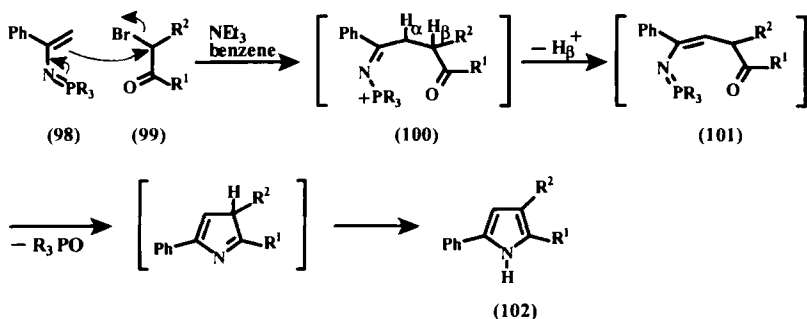


SCHEME 44

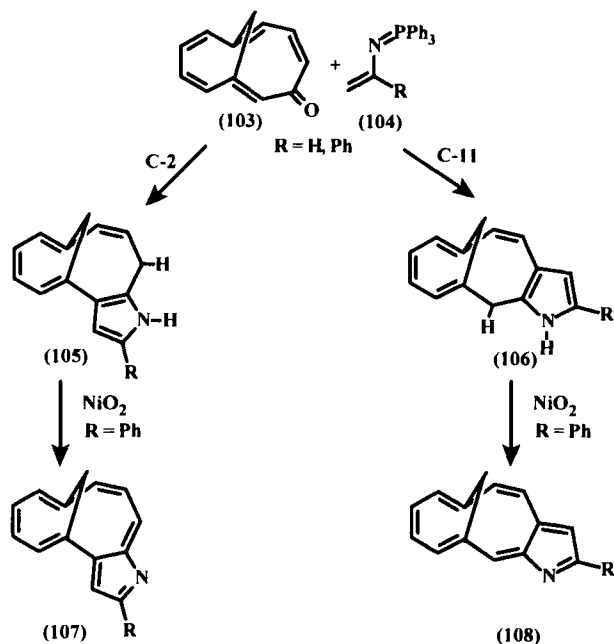
Starting with γ -azido esters, 2-alkoxypyrrolines are obtained accordingly by the same synthetic route. In an aqueous medium they are hydrolyzed to γ -lactams (86TL1031; 89TL2847; 90T1063). Nitta *et al.* have used vinyliminophosphoranes (98) for their pyrrole synthesis (Scheme 45); these are employed as enamine equivalents. After alkylation by α -bromoketones (99) in an anhydrous, acid-free medium, the β -proton of intermediate 100 is abstracted on reformation of the vinyliminophosphorane system (101). After aza-Wittig cyclization with a subsequent 1,3-H shift, pyrrole 102 is obtained [86CL463, 86H2437; 87NKK1237; 89JCS(P1)51; 90BCJ932, 90TL1291; 93MI1].

Upon application of the highly acidic α -bromocyclohexanone, the alkylation product can also lose the α -proton, leading to side products. The addition of the enolate to the $\text{C}=\text{N}$ double bond gives tetrahydrobenzofuran after removal of triphenylphosphane. The main product is formed in satisfactory quantities only when the starting material contains no substituents on the α -C atom except bromine; otherwise, the reaction of the α -bromoketone with the vinyliminophosphorane to form the alkylation adduct is sterically hindered (86H2437; 87NKK1237; 90BCJ932).

An interesting synthetic approach (Scheme 46) starts with 3,8-methano-bridged (10)-annulenones 103, which react with *N*-vinyliminophosphoranes 104. After Michael-type addition to C-2 and C-11 of the (10)-annulenone,



SCHEME 45



SCHEME 46

the condensed pyrroles **105** and **106** are formed in equal amounts. Oxidation with NiO_2 gives the aromatic 1-aza[14]annulenes **107** and **108** (90TL1291).

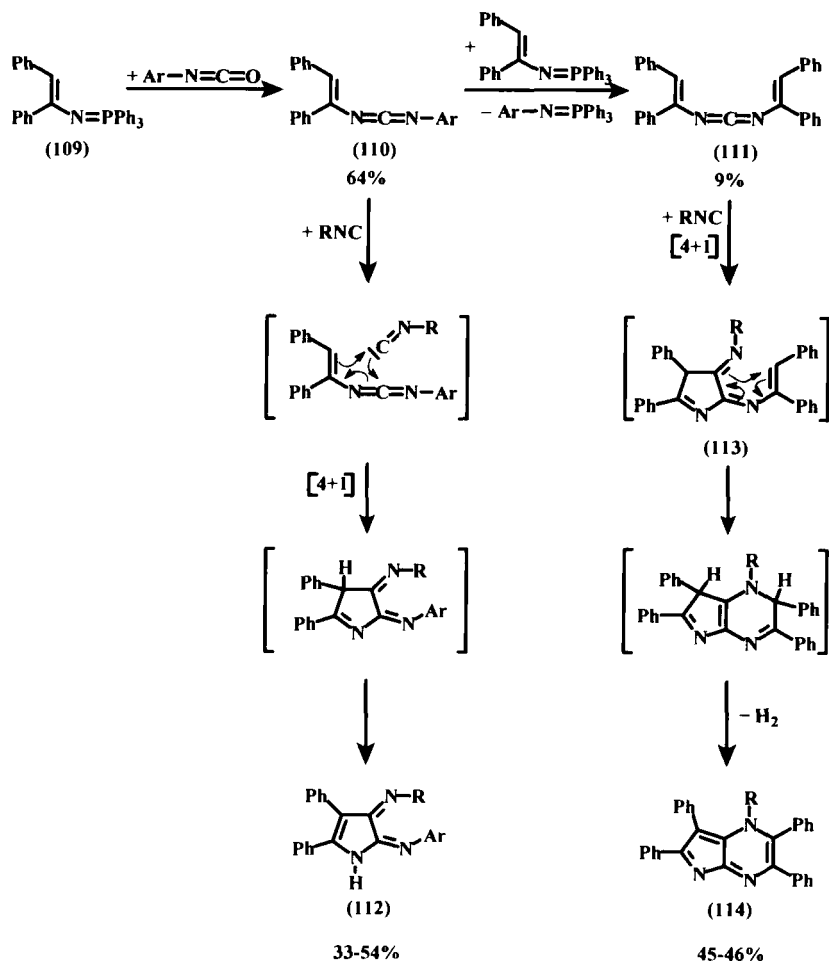
Upon reaction of *N*-vinyliminophosphoranes (**109**) with aromatic isocyanates, vinylcarbodiimides (**110**) are formed, as shown in Scheme 47. Divinylcarbodiimides (**111**) can be obtained as side products (88CB271). With isonitriles the vinylcarbodiimides also afford pyrroles (**112**) via [4 + 1]-cycloaddition. Divinylcarbodiimide can also react via [4 + 1]-cycloaddition with an isonitrile, whereupon an electrocyclic step of the initial diaza-1,3,5-trienes (**113**) follows. Finally, the pyrrolo[2,3-*e*]pyrazine **114** is obtained (88CB271).

2. Oxazoles and Thiazoles

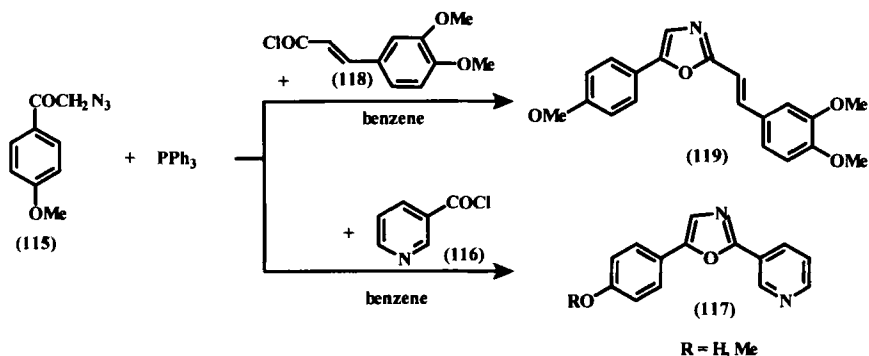
Natural product *o*-methylhalfordinol **117** is a basic principle of the oxazole alkaloids of *Halfordia scleroxyla* and *Aegle marmelos*. Annuloline **119**, a blue fluorescent pigment, has been isolated from the roots of rye stalk *Lolium multiflorum*. The total synthesis of 2,5-disubstituted oxazole alkaloids *o*-methylhalfordinol and annuloline is based on the aza-Wittig reaction (Scheme 48). Thus 4-methoxyphenacylazide **115**, triphenylphos-

phane, and nicotiny chloride **116** at room temperature directly afford *o*-methylhalfordinol. Similarly, the α -azidoketone **115** and 3,4-dimethoxycinnamoyl chloride **118** react in the presence of triphenylphosphane to give annuloline. The reaction proceeds via the initial formation of an iminophosphorane, which is then acylated. Subsequent triphenylphosphane elimination leads to the imidoyl chloride, which cyclizes to give a five-membered ring [93H(36)2255].

By the reaction of 2-azidoketones **120** with triphenylphosphane (Scheme 49), the iminophosphorane intermediate **121** is converted with isocyanate



SCHEME 47

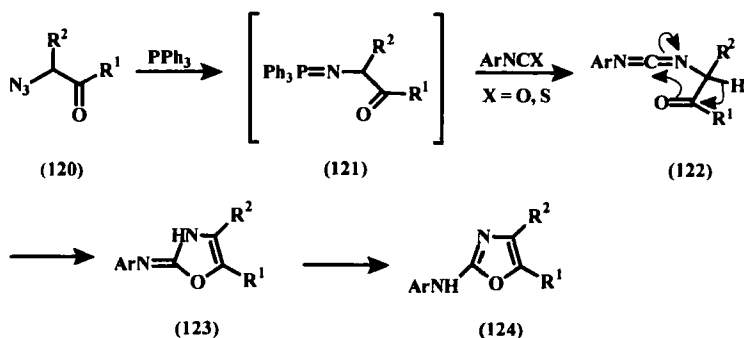


SCHEME 48

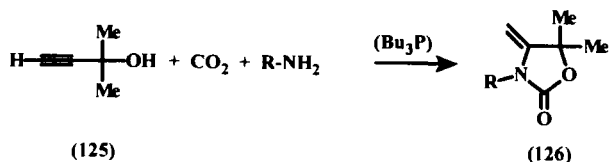
or isothiocyanate to the isolable carbodiimide **122**, which rearranges to 2-amino-1,3-oxazole **124**. Froyen explains the rearrangement of the carbodiimide, or rather the cyclization, by nucleophilic attack of the carbonyl O on the carbodiimide C, followed by a H-shift from C-1 to N. The kinetically controlled reaction leads to intermediate **123**, which tautomerizes to the thermodynamically stable 2-amino-1,3-oxazole [91PS(60)81].

An interesting 1,3-oxazol-2-one synthesis of **126** starts from propargyl alcohol **125**, CO₂, and primary amines with *n*-butylphosphane as a catalyst (Scheme 50). It is not yet clear if the phosphane reacts by formation of an iminophosphorane followed by an aza-Wittig reaction with CO₂ (90TL1721).

Aromatic acid chlorides and 2-(triphenylphosphoranylideneamino)cinnamates (**127**) give rise to 1,3-oxazol-5-ones (**129**), as shown in Scheme 51. After an intermolecular aza-Wittig reaction with **127**, the ethoxy O attacks



SCHEME 49



SCHEME 50

the imidoyl chloride of **128** and cyclizes to **129** by extrusion of ethyl chloride [90JCS(P1)1727].

For the synthesis of base-sensitive oxazoles (Scheme 52), β -acyloxyvinyl azides (**130**) react with triethyl phosphite via an aza-Wittig-cyclization. Phosphorimidate **131** is converted to 1,3-oxazole **132** with spontaneous elimination of triethyl phosphate (89JOC431). Benzoxazoles are also available by this synthetic route (71CC1608).

1,3-Oxazole-2-thiones and 1,3-thiazole-2-thiones are accessible from β -azidoalcohols employing the components triphenylphosphane/ CS_2 (90H 787).

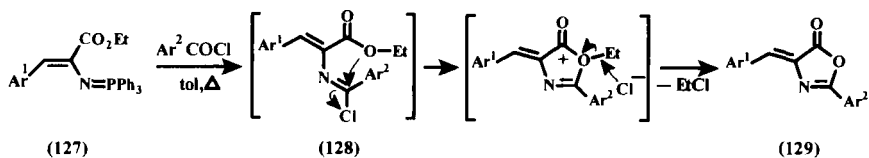
3. Pyrazoles

An intramolecular aza-Wittig reaction of 1,3-diketones (**134**) and hydrazinobis(iminophosphoranes) (**133**) gives pyrazole (**135**) on elimination of two equivalents of triphenylphosphane oxide, as shown in Scheme 53 (75CB623).

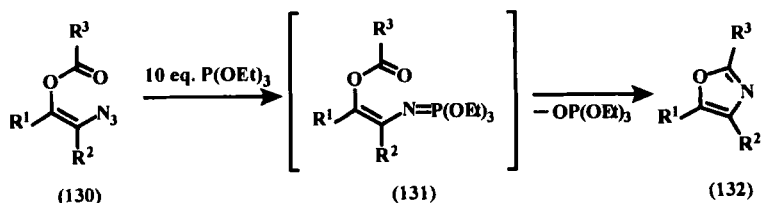
Similarly, a pyrazole synthesis occurs on addition of diazoacetic ester to diacylimine; thereby, the diazo group of the intermediate adduct is converted with triphenylphosphane into a phosphazine, which gives pyrazole as described above (68TL4371).

4. Imidazoles

Imidazoles are synthesized from *N*-(2-azidoethyl)phthalimide (**136**) via the Staudinger reaction to obtain an initial intermediate iminophosphorane **137**, which is then converted by an intramolecular aza-Wittig reaction and



SCHEME 51



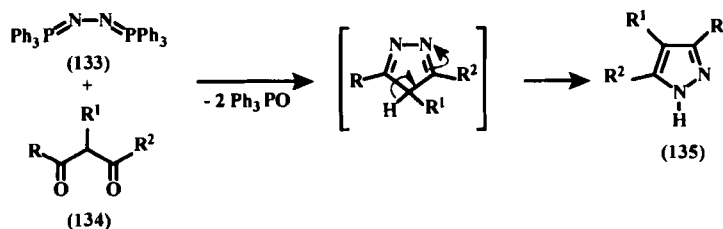
SCHEME 52

elimination of triphenylphosphane oxide into the condensed imidazoline **138**, as shown in Scheme 54 (89CC602). This concept can be transferred to α -azido carboxylic imides, whereby imidazolin-5-ones as well as imidazoles are obtained, both as part of a macrocyclic ring (89T6375).

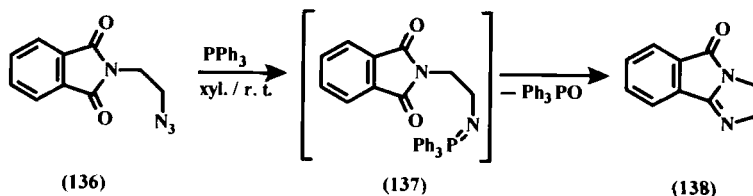
A broad choice of 1,4,5-trisubstituted imidazoles can be prepared with the aid of the novel synthon BETMIP (**68**) and primary amines, as shown in Scheme 55. The resulting intermediate **139** reacts without isolation directly with α -diarylketones (**140**) to afford 1-substituted 4,5-diarylimidazoles (**141**). Cycloheptylamine, benzylamine, dodecylamine, and 4-dimethylaminoaniline can be employed as amines. Reactive 1,2-diketones include benzil, 4-chlorobenzil, and 9,10-phenanthrenequinones (90H2187).

The use of BETMIP as a synthetic equivalent for $^+\text{CH}_2=\text{N}$ is shown in Scheme 56.

Benzimidazoles occurring as constituents of vitamin B_{12} in nature are of preparative interest due to their high biological activity. Thus, 1-(butylaminocarbonyl-2-methoxycarbonylamino)benzimidazole and 2-(thiazol-4-yl)benzimidazole are widely used as fungicides, the latter additionally as a preservative for fruits (E 233). This class of compounds can be prepared by an aza-Wittig reaction, as shown in Scheme 57. 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one (**144**) is prepared both via *N*-(2-azidoaryl)succinimide (**142**) (90TL6561) and via *N*-(2-aminophenyl)-2,5-pyrrolidinedione (**143**) (88JHC1047). The only difference is the nature of the iminophosphorane generation: In the first case, **142** is formed in the



SCHEME 53

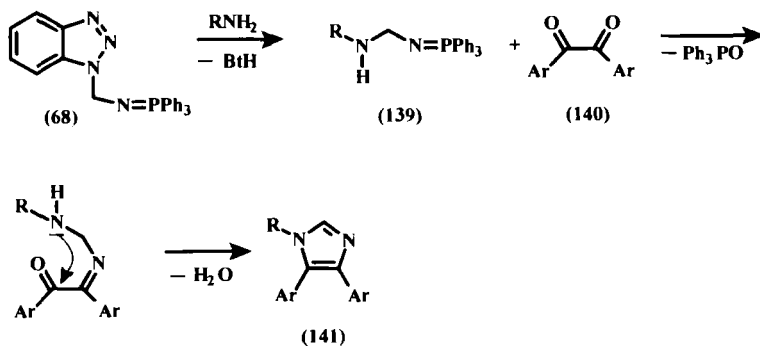


SCHEME 54

classical way via a Staudinger reaction; in the second case, **143** is formed by reaction with dibromotriphenylphosphorane/triethylamine. In both cases, intramolecular cyclization occurs.

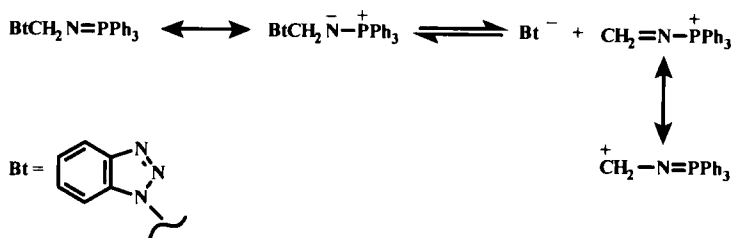
Starting from acylated 2-azidomethylbenzimidazoles (**145**), an additional imidazole ring can be condensed by transformation of the azido group with tri-*n*-butylphosphane into the appropriate iminophosphorane intermediate **146**. After extrusion of phosphane oxide, cyclization occurs to the 1-substituted 4*H*-imidazo[1,5-*a*]benzimidazole **147** (Scheme 58) (89T1823; 94S1197).

When simple substituted benzimidazoles such as 2-azidomethyl benzimidazole are employed, their iminophosphoranes (**148**) react with isocyanate to give carbodiimide **149**. The free NH group of the imidazole can intercept the carbodiimide intermolecularly. Thus, upon addition of a second equivalent of isocyanate, cyclization affords 2,3-dihydro-1*H*-imidazo[1,5-*a*]benzimidazole **150** (Scheme 59) (89T1823; 94S1197).



Bt = Benzotriazole

SCHEME 55



SCHEME 56

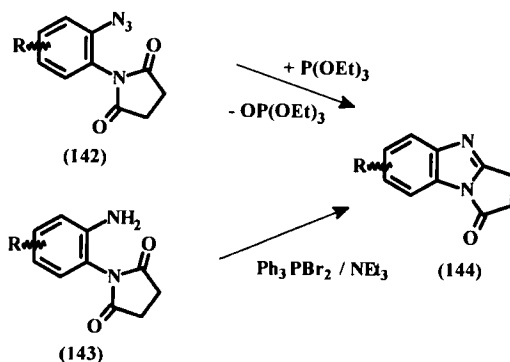
5. 1,3,4-Oxadiazoles

1,3,4-Oxadiazoles are obtained by reaction of aromatic isocyanates or CS₂ with *N*-acylaminoiminophosphoranes (**151**), as shown in Scheme 60. Upon treatment with isocyanate, an unstable carbodiimide **152** is generated, which cyclizes spontaneously in 80–84% yield. With CS₂ as reagent, the corresponding isocyanate cyclizes without isolation of any intermediates to 2-mercapto-1,3,4-oxadiazole **154** in 72–90% yield [91PS(57)11].

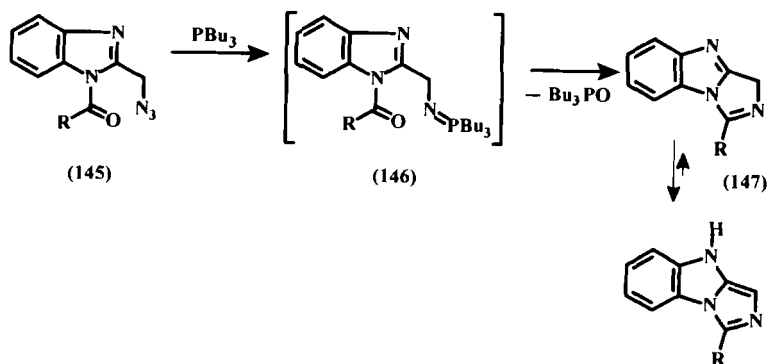
Another preparation of oxadiazoles proceeds from *N*-acylaminoiminophosphorane as well. With diphenylketene, an intermediate ketenimine (**155**) is converted to 2-diphenylmethyl-1,3,4-oxadiazole **156** (Scheme 61) [91PS(63)283].

With phenyllithium, the iminophosphoranes of benzoic acid hydrazides **157** can be deprotonated, as shown in Scheme 62. *O*-Acylation of the amide-enolates **158** affords intermediates **159**, which are in turn cyclized by an aza-Wittig reaction to 1,3,4-oxadiazoles **160** (68JA5626).

Mesoionic oxadiazoles are available from 2(1*H*)-pyridones and methyl isocyanate via carbodiimide (88CB1495).



SCHEME 57

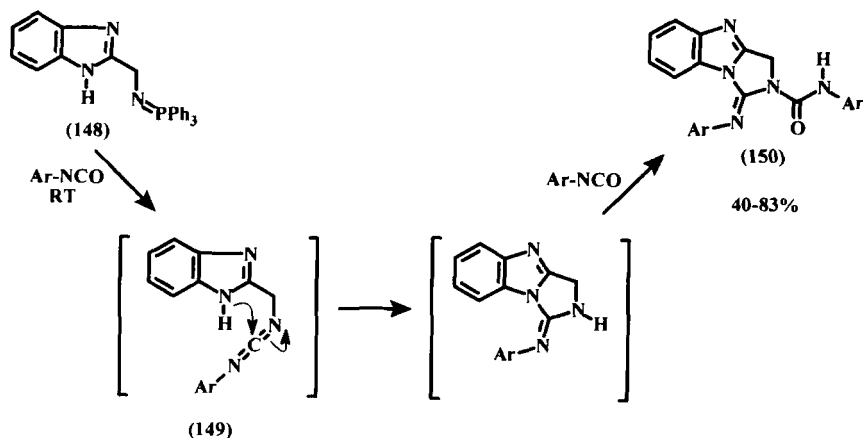


SCHEME 58

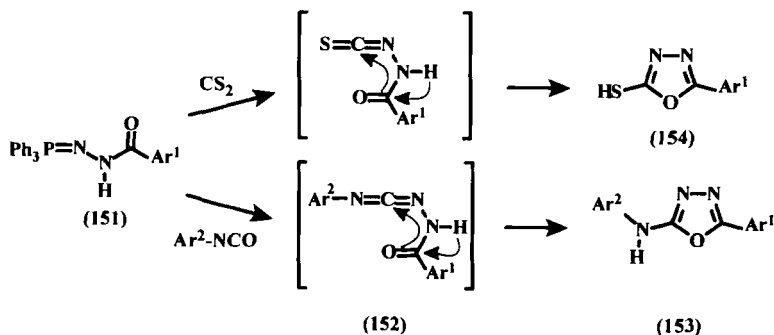
6. 1,3,4-Thiadiazoles

From the reaction of imidazole **161** and aromatic acid halides (Scheme 63), imidoyl chlorides **162** are obtained, which eliminate methyl chloride to form imidazo[2,1-*b*]1,3,4]thiadiazoles **163** upon extended heating (88H1935).

Under much milder conditions, the same reaction occurs with 1,2,4-triazinone **164**, resulting in the formation of a 1,3,4-thiadiazolo[2,3-*c*][1,2,4]triazinium cation **165** (Scheme 64) (88H1935). Another cationic product is obtained upon conversion of dithiocarbazate to carbodiimide, which occurs via iminophosphorane formation and aza-Wittig reaction with



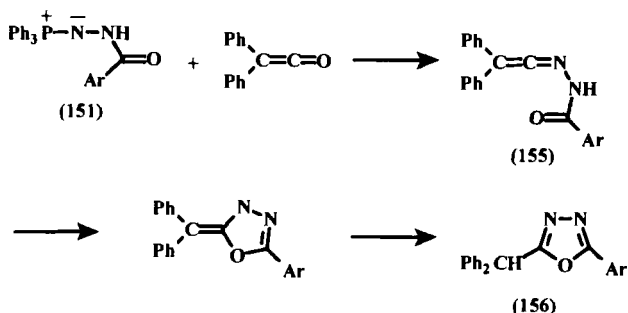
SCHEME 59



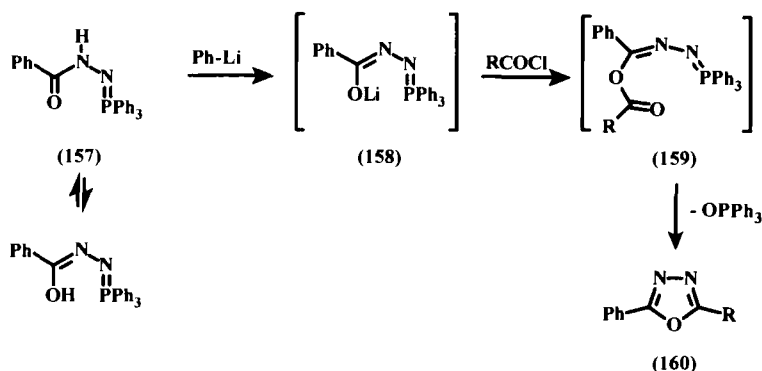
SCHEME 60

isocyanate. Direct cyclization and protonation affords 1,3,4-thiadiazolium salts [89S923; 91JCS(P1)1159].

In the case of thiazoline-2(3*H*)-thiones, the mesoionic thiazolo[2,3-*b*][1,3,4]thiadiazoles are obtained by two different routes (Scheme 65). On the one hand, thione **166** reacts with isothiocyanate via intermediate **167** and with a second equivalent isothiocyanate to afford the mesoionic **168**; on the other hand, in the presence of isocyanate, the thione preferentially dimerizes **167** with the open-chain carbodiimide **169** to give the mesoionic **170**. Addition of acid with removal of an amine group converts **170** into the symmetric heteroaromatic amine (**171**) (88CB1495; 92T1285). The related transformation of an imidazoline into 1,3,4-thiadiazoles has also been described (90T4353).



SCHEME 61



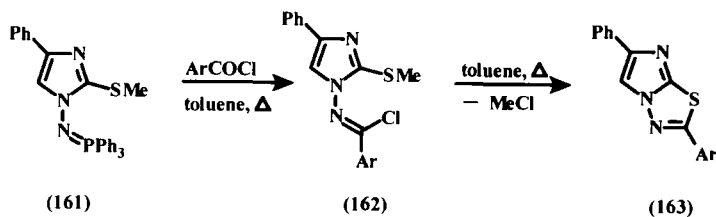
SCHEME 62

7. 1,2,4-Triazoles

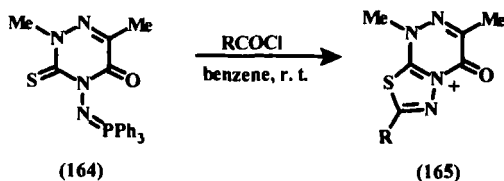
Phosphorylated 2,3-diamino-2*H*-indazoles (**172**) are well suited for the annulation of a 1,2,4-triazole ring by a combination of an aza-Wittig and an intramolecular trapping reaction. As shown in Scheme 66, CS₂ and CO₂ are good reaction partners; in the case of acid halides, however, no ring closure occurs, and **173** was obtained [89TL6237; 90JOC4724].

A direct aza-Wittig cyclization to triazototriazine **176** (Scheme 67) takes place when triazinone **174** is treated with diphenylthiourea, the latter being substituted on the nitrogen. Elimination of triphenylphosphane sulfide from **175** makes 1,2,4-triazole accessible [86JCS(P1)2037]. When the nucleophilic attack continues on the sulfur, thiadiazoles are formed [86JCS(P1)2037].

The iminophosphorane **177** available from methyl azido(phenylhydrazono)acetate by a Staudinger reaction represents an ideal starting material for the synthesis of 1*H*-1,2,4-triazoles (**180**). Two synthetic routes are possible (Scheme 68). The first is the reaction of iminophosphoranes with halides via isolable *N*-acylphosphonium salts (**178**), and imidoyl chlorides (**179**), leading to triazoles. The other approach involves the less reactive anhy-



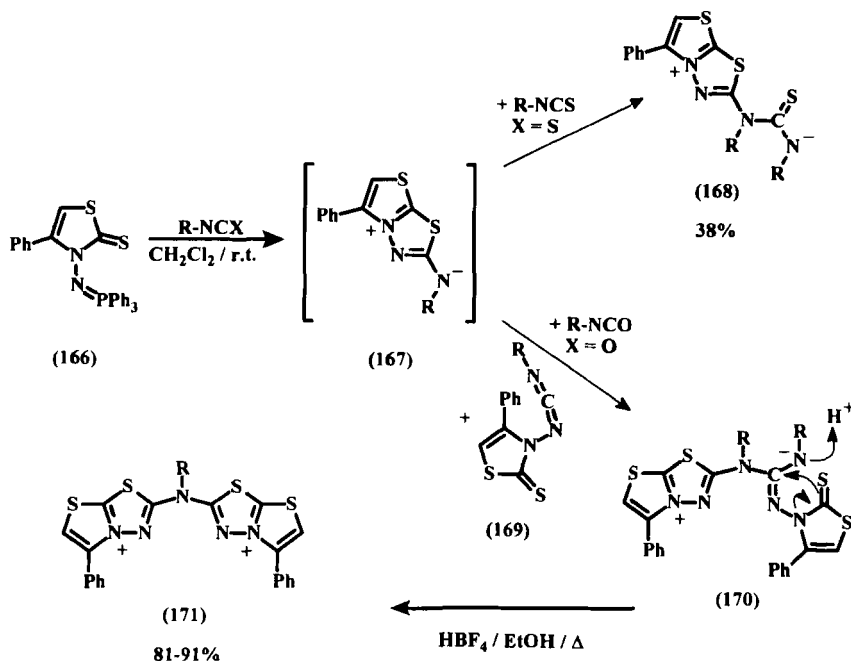
SCHEME 63



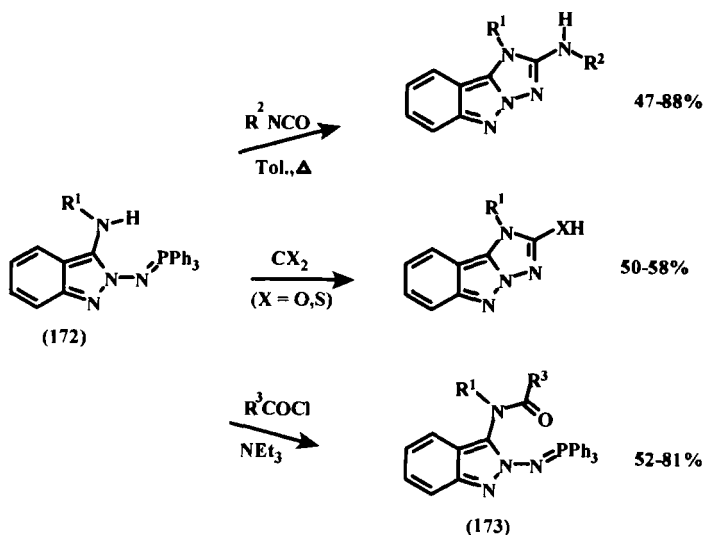
SCHEME 64

drides, e.g., succinic anhydride **181**, to afford triazole derivatives, such as **182** [86S772; 89JCR(S)16].

An aza-Wittig reaction with carbonyl electrophiles, accessible from iminophosphorane (**177**) and aldehydes, gives 5-alkyl- or 5-aryl-1*H*-1,2,4-triazoles (Scheme 69) (85S304). The reaction of **177** with isocyanate generates two different products, both of which occur from primary adduct **183** following elimination of both an iminophosphorane and triphenylphosphane oxide. In the latter case, 5-alkylamino- or 5-arylamino-1*H*-1,2,4-triazole **185** is formed from carbodiimide **184**. The elimination of iminophosphorane is only worth mentioning when the relatively stable *N*-



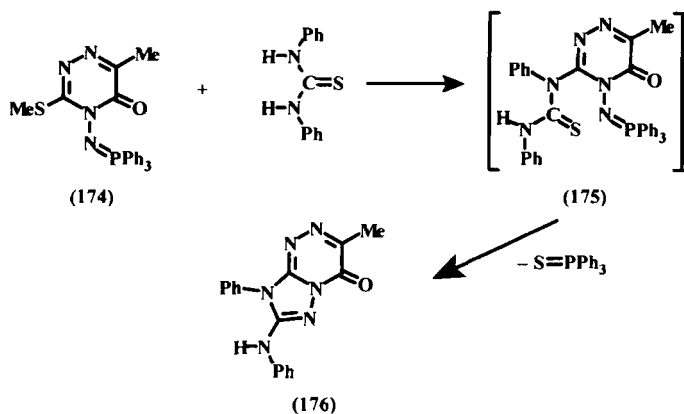
SCHEME 65



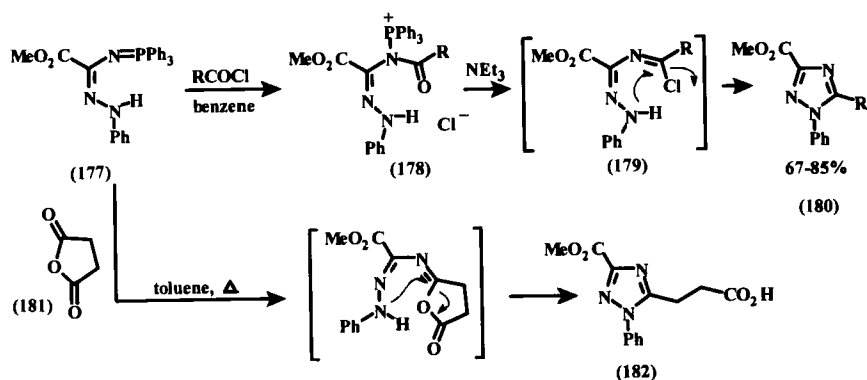
SCHEME 66

aryliminophosphorane can be formed; in this case, triazolones **186** can be isolated [86JCS(P1)2177].

The syntheses of bis-1,2,4-triazole start with diamidrazone **187** formed by reduction of diazide **188** with LiAlH_4 in ether (Scheme 70). Furthermore, **188** is converted with the aid of the Staudinger reaction into bisimino-



SCHEME 67

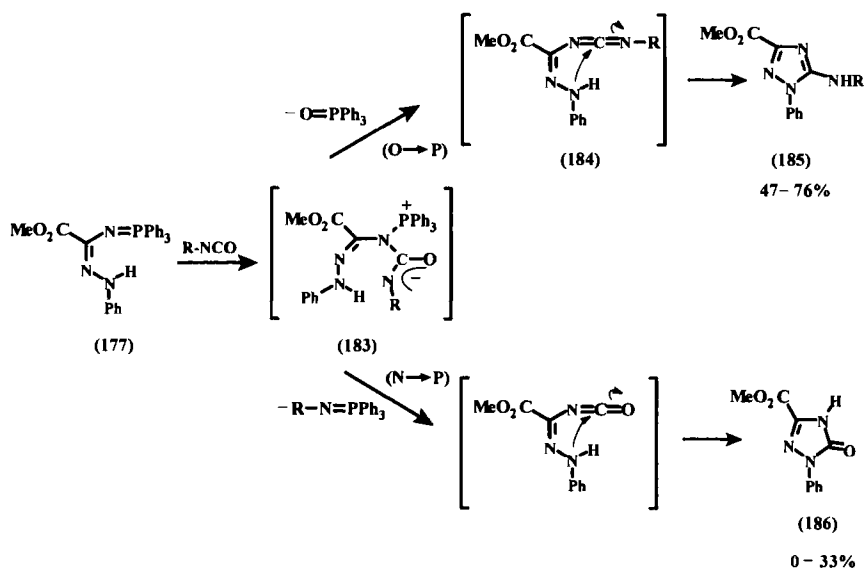


SCHEME 68

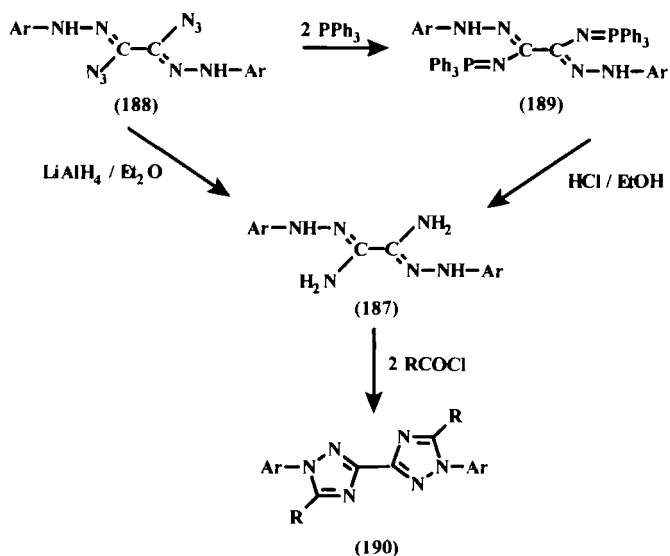
phosphorane **189**, which gives a diamidrazone after acid hydrolysis. Upon treatment with two equivalents of acid chloride, **187** (which is obtained by these both approaches) affords the bis-1,2,4-triazole **190** (93T2761).

8. Tetrazoles

The use of the aza-Wittig reaction as a synthetic pathway to tetrazoles has been little described. One communication reports the reaction of imino-

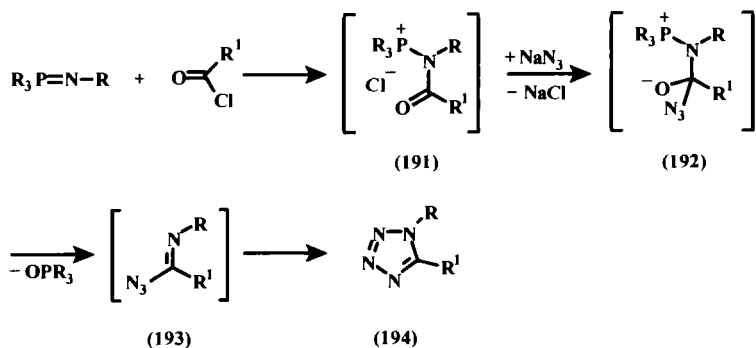


SCHEME 69



SCHEME 70

phosphoranes with acid chlorides in the presence of sodium azide (Scheme 71). The zwitterion **192** obtained from *N*-acylaminophosphonium salt **191** reacts, after elimination of triphenylphosphane oxide, to form a nonisolable iminoazide (**193**), which undergoes spontaneous ring closure to tetrazole **194** (69LA29).



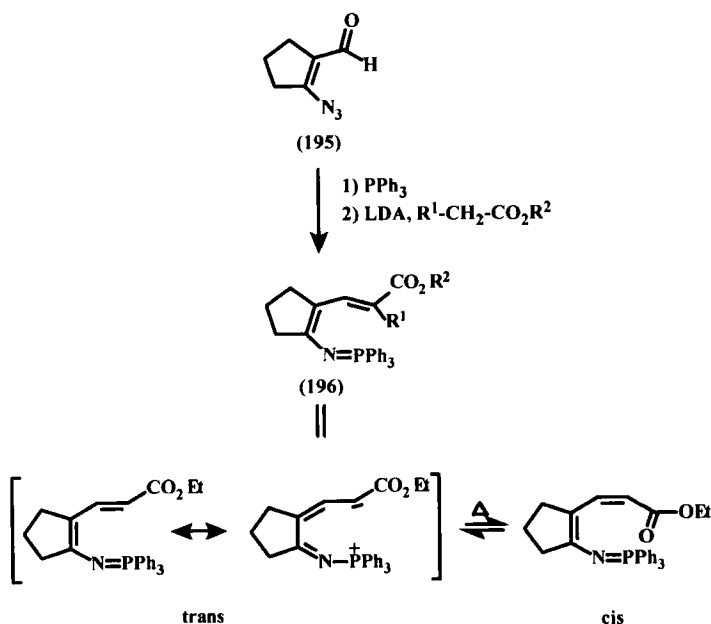
SCHEME 71

D. SIX-MEMBERED HETEROCYCLES

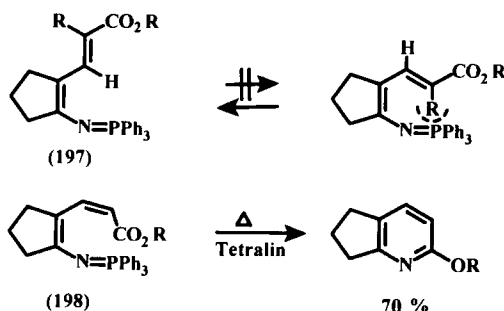
1. *Pyridines*

In addition to the cycloaddition–ring-enlargement (CARE) principle (83CB1691; 85AHC299, 85CB863; 86CB2114, 86CB3515, 86JOC149), the intramolecular aza-Wittig strategy is often used. In this strategy, δ -Azido-1,3-dicarbonyl compounds afford vinylogous cyclic urethanes or carbonamides (85JOC535). In the presence of triphenylphosphane δ -azidoketones cyclize under anhydrous conditions to give 3,4,5,6-tetrahydropyridines (85JOC535). This principle can also be applied to complex substrates (70M508; 83JA5912; 87H3265; 90JA291).

With the aid of a Knoevenagel condensation and a Staudinger reaction, 2-azidocyclopent-1-ene 1-carbaldehydes (**195**) can be converted into suitable products for a cyclopenta[*b*]pyridine synthesis [89JCS(P1)1369], as shown in Scheme 72. In order to bring the ester carbonyl function and the imino-phosphorane group into close proximity suitable for cyclization reactions, the 1,3-diene system **196** should possess the *s-cis* conformation. Furthermore, the exocyclic double bond should show a *cis* conformation. To achieve



SCHEME 72



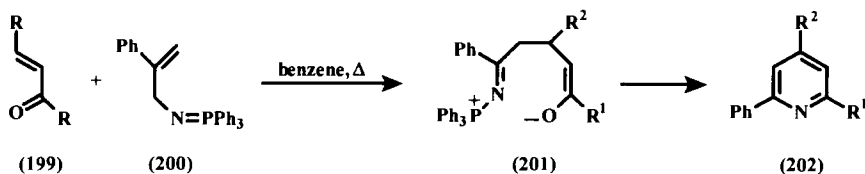
SCHEME 73

a thermal *trans* \rightarrow *cis* isomerization of **196**, application of a high temperature is necessary [89JCS(P1)1369].

As shown in Scheme 73, a substituent α to the carbonyl group hampers the formation of the cyclopenta[*b*]pyridines, as the *s-cis* conformation of **197** is sterically unfavorable. This limits the synthesis to 3-unsubstituted derivatives **198** only [89JCS(P1)1369].

An interesting synthetic concept involves *N*-vinyliminophosphoranes (**200**) and α,β -unsaturated ketones (**199**) or aldehydes, wherein **200** is added in a kind of Michael reaction to ketones or aldehydes (Scheme 74). Imino-phosphorane and carbonyl groups then perform a spontaneous intramolecular cyclization to afford 3,4-dihydropyridines, which are oxidized by excess Michael adduct to form pyridines **202** [86CL1549; 87NKK-1237; 88CBCJ2235; 90JCS(P1)1119]. The yield depends significantly on the substituent pattern; ketones produce higher yields than aldehydes do. The synthetic potential of this reaction follows from the many varieties of *N*-vinyliminophosphoranes and α,β -unsaturated ketones [88TL5957; 89BCJ2401; 90BCJ932, 90JCS(P1)435, 90JCS(P1)1119; 93MI1]. A recent review describes the syntheses of *N*-heterocycles via vinyliminophosphoranes (93MI1).

Access to pyridines from aza-1,3,5-triene units, achieved by an intramolecular aza-Wittig reaction and thermal electrocyclic cyclization with a subsequent 1,3-H shift, was mentioned in Section V,B (cf. Scheme 28) as an



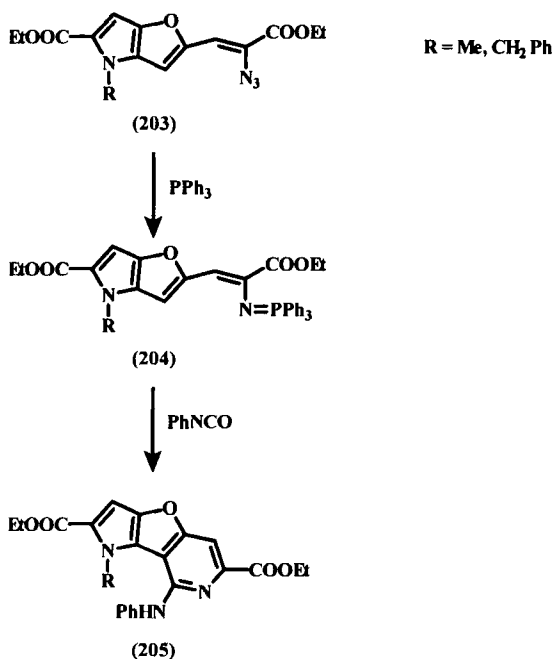
SCHEME 74

example of a "tandem aza-Wittig reaction." This general strategy has been used by Molina *et al.* in the syntheses of several pyridines and heterocondensed pyridines [87S45; 88JCS(P1)1819, 88JOC4654, 88TL379; 89CB307, 89S878; 90S474; 92TL4491; 94S1197].

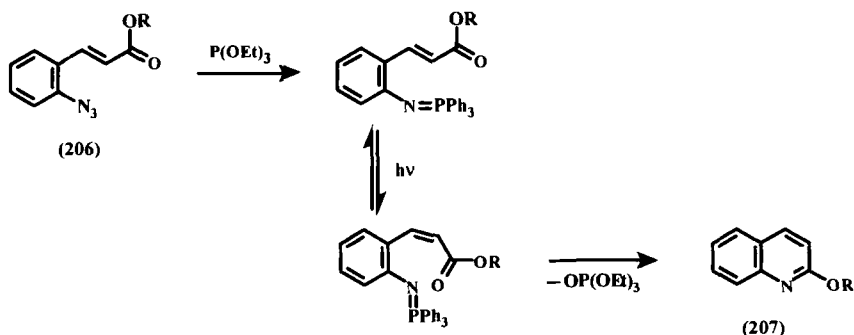
Some recent work has made several heterocondensed furo[3,2-*c*]pyridines accessible. Starting compounds are the aldehydes of furo[3,2-*c*]pyridines, which are converted into the azides **203** (Scheme 75). Reaction with triphenylphosphane furnishes the iminophosphoranes **204**, which are finally cyclized with phenyl isocyanate to afford the substituted pyrrolo[2',3':4,5]-furo[3,2-*c*]pyridines **205** (92M807; 94H1695).

2. Quinazolines

Quinazolines have become increasingly important as biologically active principles, e.g., as antiseptics or antimalarials. An interesting approach to this class consists of a combination of the aza-Wittig reaction with photochemical processes, as shown in Scheme 76. *o*-Azidocinnamates (**206**) are cyclized with the aid of triethyl phosphite to afford 2-alkoxyquinolines



SCHEME 75



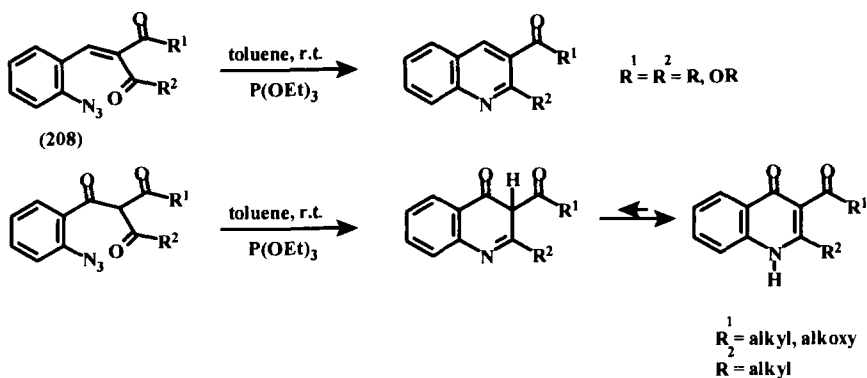
SCHEME 76

(207); the *trans*–*cis* isomerization needed for this cyclization is effected photochemically (73CC29).

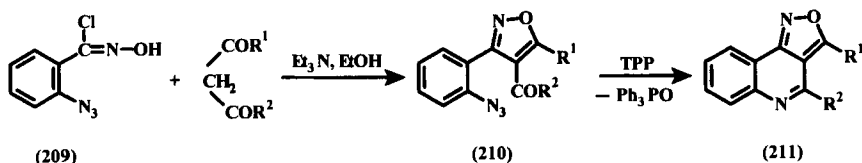
No isomerization is necessary when another carbonyl function is present in an α -position (cf. **208** in Scheme 77). When both ester and keto functions can undergo aza-Wittig cyclization, the more electrophilic keto group is preferred (90TL6561).

Another approach to the syntheses of quinazolines involves 3-(*o*-azidophenyl)isoxazoles (**210**) which are accessible from α -chloro-2-azido benzaloximes (**209**) and β -keto esters ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{OEt}$). As shown in Scheme 78, the iminophosphorane resulting from the Staudinger reaction is transformed without isolation by an aza-Wittig reaction into 3,4-disubstituted isoxazolo[4,3-*c*]quinolines (**211**) (92MI1).

This synthesis can be adapted to several other azido systems. For example, in Scheme 79 *o*-azidophenylnitrones (**212**) undergo 1,3-dipolar cycloaddi-



SCHEME 77



SCHEME 78

tion with dimethyl acetylenedicarboxylate (DMAD) to give an isoxazoline adduct (**213**). A subsequent Staudinger reaction with triphenylphosphane and an intramolecular aza-Wittig reaction afford 1,9-dihydroisoxazolo[4,3-*c*]quinolines (**214**) (92MI1).

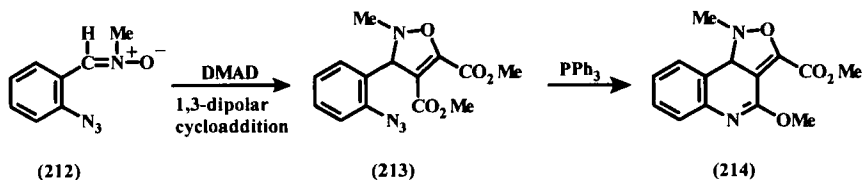
An easy one-pot procedure (Scheme 80) gives pyrimido[4,5-*b*]quinolines by reacting the iminophosphorane **215** prepared from *o*-azidobenzaldehyde with *N,N*-dialkylbarbituric acid (**216**). Refluxing in pyridine leads to the elimination of phosphane oxide and to quinoline **217** (92S827).

Quinolines are also formed via the tandem aza-Wittig/6 π -electrocyclization procedure (92JOC929). Furthermore, Saito *et al.* reported a facile conversion of conjugated carbodiimides into quinolines by an intramolecular cycloaddition (92CC22; 93CC1802). In the presence of a Lewis acid, the conjugated carbodiimides react smoothly as 2-azadienes with several dienophiles, e.g., aldehydes, acetylenic compounds, enamines, and vinyl ethers, to give nitrogen cycloadducts (93CL1127).

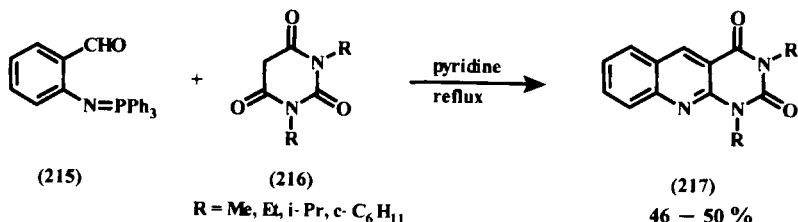
3. Isoquinolines

The aza-Wittig/6 π -electrocyclization strategy for the synthesis of 1-arylaminisoquinolines **220** was applied for the first time by Saito *et al.* (86CL135). This sequence (Scheme 81) is induced by an aza-Wittig reaction of *N*-vinyliminophosphoranes **218** with isocyanates. The vinylcarbodiimides **219**, once formed, spontaneously undergo thermal 6 π -electrocyclization (86CL135).

The ease of this thermal 6 π -electrocyclization depends on the electron density within the aromatic ring. With weak electron donors, temperatures



SCHEME 79

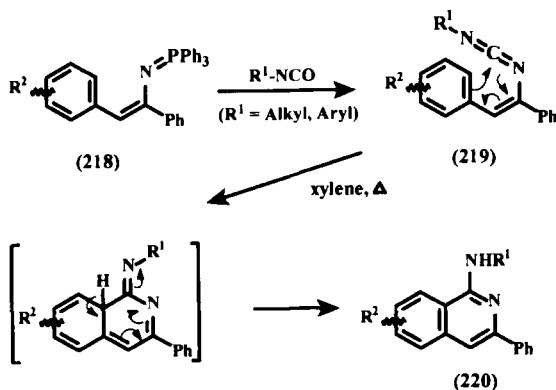


SCHEME 80

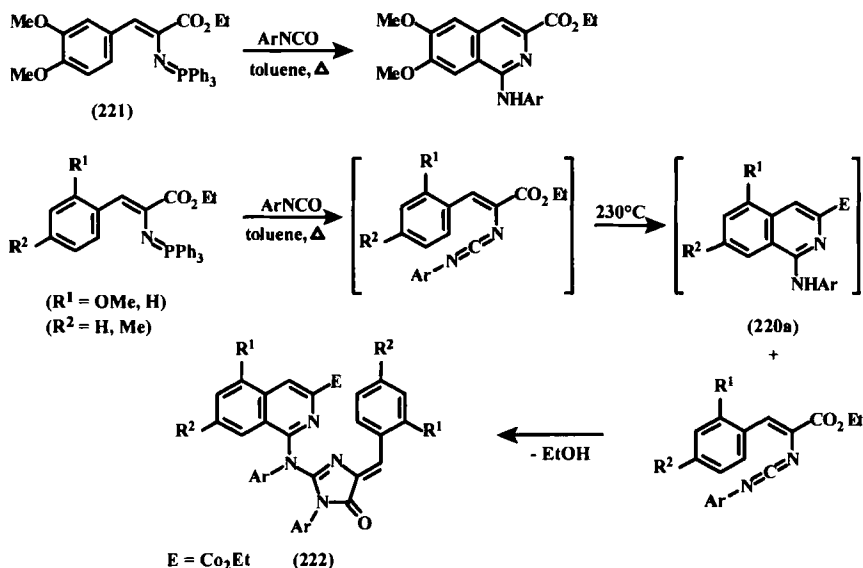
above 200°C are necessary, while isoquinolines are generated by simple heating in toluene, the aromatic ring being substituted with two methoxy groups (**221**) [90JCS(P1)1727]. In the presence of weak electron-donating substituents at the aromatic ring, the cyclization tendency is considerably reduced, so that 1-arylisquinoline (**220a**) adds to unreacted carbodiimide to afford unsymmetric dimers (**222**), forming an additional imidazole ring [90JCS(P1)1727]. (See Scheme 82.)

Rees *et al.* have developed mild reaction conditions and high yields for their isoquinoline syntheses. Starting with 2-azidocinnamic esters **223**, which have been converted with the aid of a Staudinger reaction into the iminophosphoranes, the carbonyl function in an *o*-position enables a subsequent intramolecular aza-Wittig reaction, as shown in Scheme 83 [79CC627; 87JCS(P1)921, 87JCS(P1)1395]. Since no additional electron donors on the aromatic ring are necessary in this case, more complex substrates can be employed [79CC627; 87JCS(P1)921].

Using the tandem aza-Wittig/6 π -electrocyclization strategy, an isoquinoline synthesis starts with salicylaldehyde, which is converted with azido-



SCHEME 81

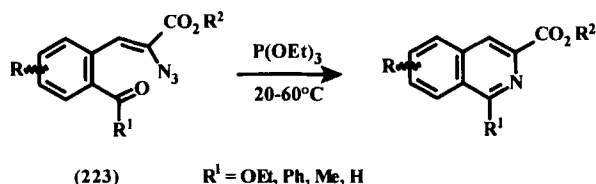


SCHEME 82

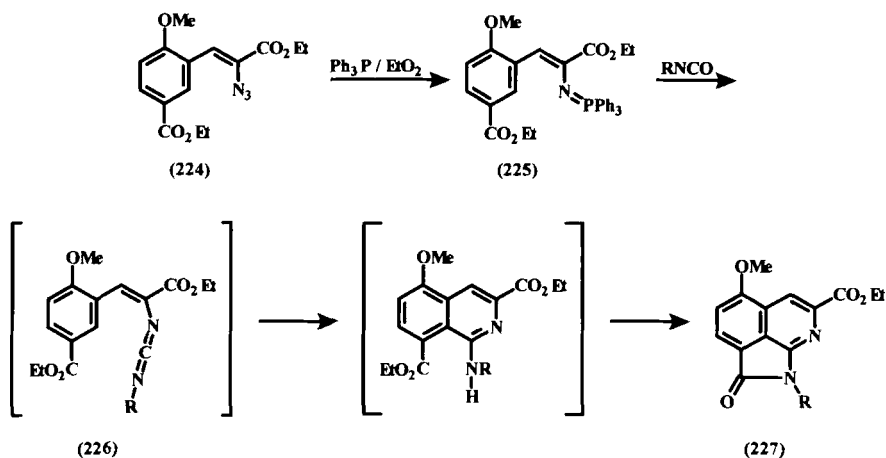
acetate into azide **224**. Iminophosphorane (**225**) forms with triphenylphosphane, then subsequent aza-Wittig reaction with isocyanate gives, via 6 π -electrocyclization and a 1,3-H shift, pyrrolo[4,3,2-*i*]isoquinoline (**227**), as shown in Scheme 84 (92S293).

4. Oxazines and Benzoxazines

The syntheses of simple 1,3-oxazines (74AG596; 86G361) from acylated amino acids (86G361) by treatment with dihalotriphenylphosphorane and of heterocondensed 1,3-oxazin-4-ones from several *N*-acylated heterocyclic β -enamino esters (81CB3188) have been implemented by aza-Wittig reactions of heterocyclic 2-(triphenylphosphoranylidenamino)esters with acid halides.



SCHEME 83

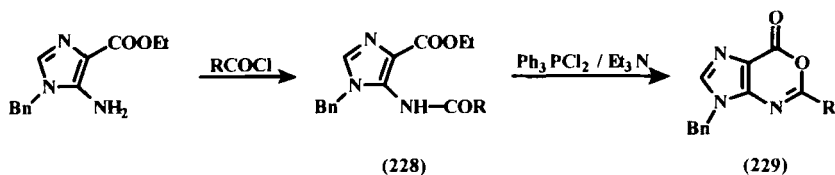


SCHEME 84

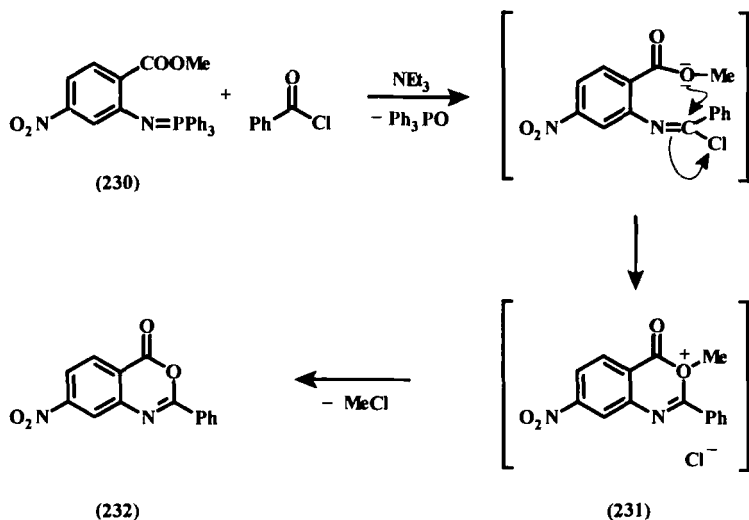
The easily accessible aroylaminoimidazole-4-carboxylates (**228**) give imidazo[4,5-*d*][1,3]oxazin-7-ones (**229**) in a novel cyclization with dichlorotriphenylphosphorane (Scheme 85) (93S107). Heterocyclic β -enamino esters, such as 5-amino-2-(methylthio)thiazole-4-carboxylates and 4-amino-2-(methylthio)thiazole-5-carboxylates can also be used; in both cases 1,3-oxazine rings are smoothly condensed to the existing heterocyclic ring (93S107).

Benzocondensed 3,1-oxazin-4-ones are also accessible via an aza-Wittig reaction (Scheme 86) (93T581). Iminophosphorane **230** affords an imidoyl chloride with aroyl chlorides. The electrophilic C atom is attacked by the ester methoxy group, and the formation of a six-membered ring **231** is thermodynamically favored. Extrusion of methyl chloride gives the stable benzoxazinone **232** (93T581).

Employing ynamines, the cycloaddition–extrusion reaction can be extended to heterocondensed 1,3-oxazinones, resulting in a smooth, simple annulation of a pyridine ring to an existing heterocyclic system (87CB1427).



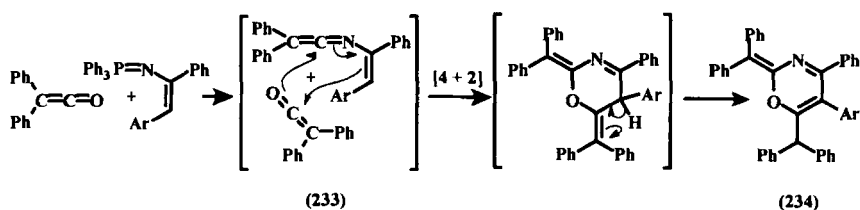
SCHEME 85



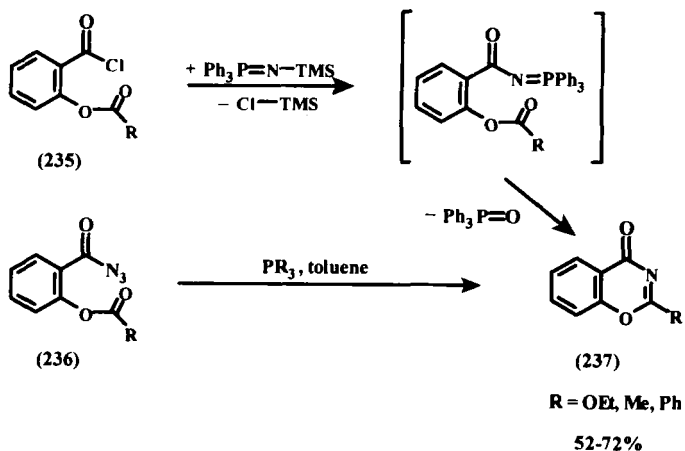
SCHEME 86

A novel heterocyclic system has been achieved from methyl 3-aminopyrazine-2-carboxylate and several aroyl chlorides, leading to 3-arylamino derivatives; the latter are cyclized with dibromotriphenylphosphorane to 2-arylpyrazino[2,3-*d*][3,1]oxazin-4-one (94S405). Furthermore, vinyliminophosphoranes and diphenylketene react (Scheme 87) to give nonisolable vinylketenimines (233) which afford, with a second equivalent of ketene in a [4 + 2]-cycloaddition, 1,3-oxazinones (234) [89JCS(P1)2140].

1,3-Benzoxazin-4-ones (237) are produced by reaction of 2-acyloxybenzoic azides 236 and phosphane (Scheme 88) (81S816; 85CB4632). Employing triphenylphosphane, the *N*-acyliminophosphorane intermediate can be isolated at room temperature. With tributylphosphane, cyclization occurs immediately (81S816; 85CB4632). Alternatively, benzoxazin-4-ones can be prepared directly from 2-acyloxybenzoyl chloride (235) and *N*-trimethylsilyliminophosphorane (87BSF997).

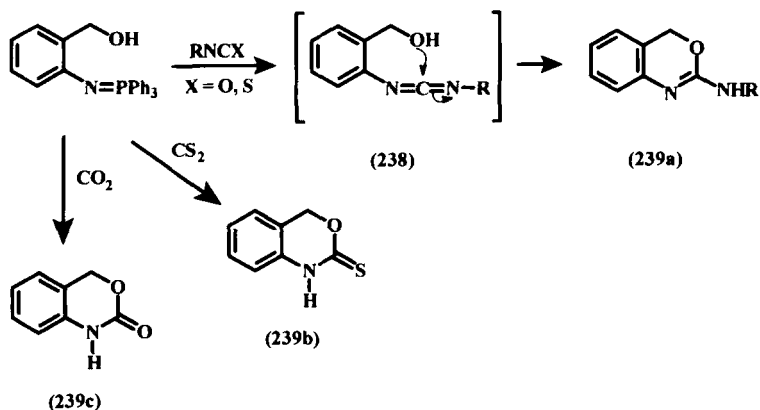


SCHEME 87



SCHEME 88

Finally, the synthesis of 4H-3,1-benzoxazines **239** via a tandem aza-Wittig reaction (Scheme 89) should be mentioned. Carbodiimide **238** or isocyanate generated by an intramolecular aza-Wittig reaction bears an *o*-hydroxymethyl group on the *N*-aryl substituent; this OH attacks the carbodiimide C intramolecularly with cyclization to give a 3,1-benzoxazine (91S21).



SCHEME 89

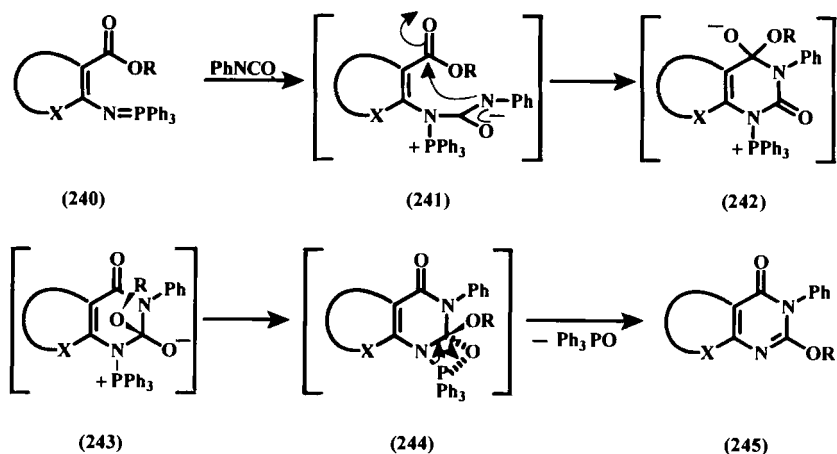
5. Pyrimidines

One of the most important species of six-membered heterocycles is represented by the pyrimidine group. Simple synthetic approaches therefore are of great importance.

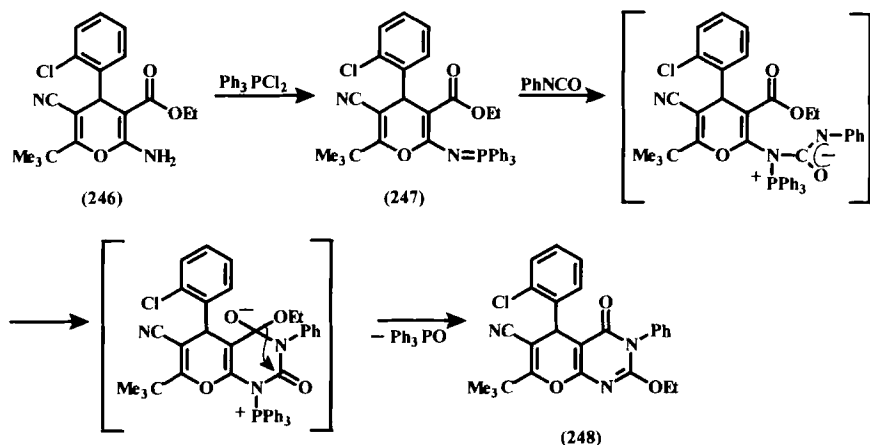
Recently, Wamhoff *et al.* have developed a novel and general type of pyrimidine annulation to an existing heterocyclic ring by employing heterocyclic 2-(triphenylphosphoranylideneamino) esters (**240**) and isocyanates (Scheme 90). In this special case, the expected carbodiimides could not be monitored as no heterocumulene bands were found in the IR spectra. X-Ray analysis revealed that a new pyrimidine ring had been annulated with a 2-alkoxy group stemming from the former 3-ester position. Thus, after primary addition of isocyanates to **241** in a complex cyclization mechanism, $4 \rightarrow 2$ alkoxide migration (**242** \rightarrow **244**) occurred, followed by triphenylphosphane oxide extrusion to form **245** (90LA901, 90LA995).

The synthesis of 4*H*-pyrano[2,3-*d*]pyrimidines, a class of compounds important in crop protection, is presented in Scheme 91. Dichlorotriphenylphosphorane affords iminophosphorane **247** with ethyl 2-amino-4*H*-pyran-3-carboxylate (**246**). Phenyl isocyanate cyclizes under alkoxide migration to afford pyrano[2,3-*d*]pyrimidines (**248**) (90LA995).

In another approach (Scheme 92) enamino nitriles **249** serve as starting materials for pyrimidine syntheses. After transformation with triethyl orthoformate to 2-ethoxymethylenimino-3-carbonitriles (**250**), these are cyclized with semicarbazide to pyrano[2,3-*d*]pyrimidin-3-yl ureas (**251**). Dichlorotriphenylphosphorane reacts in a second cyclization to give 1,2,4-triazolo[1,5-



SCHEME 90

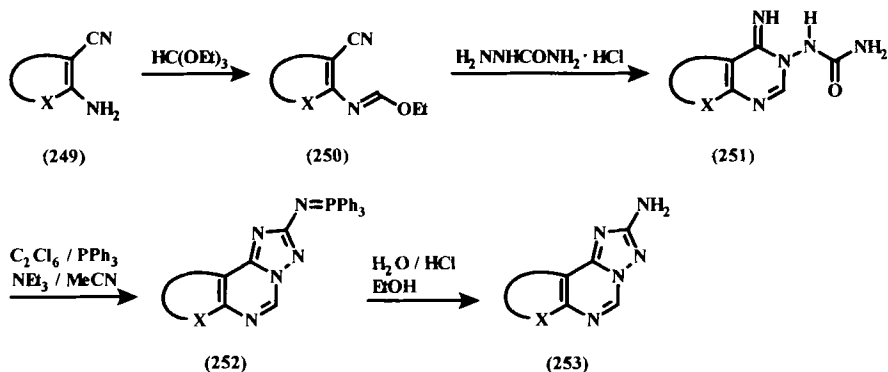


SCHEME 91

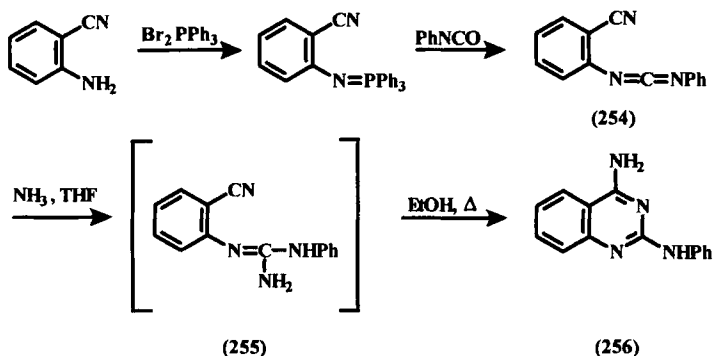
c]pyrimidine (**252**). The iminophosphorane group can be hydrolyzed to afford free amine **253** (93S1129).

Taylor and Patel describe a quinazoline synthesis (Scheme 93) transforming the iminophosphorane of anthranonitrile with isocyanate to carbodiimide **254**. Addition of ammonia in tetrahydrofuran (THF) leads to guanidine **255**, which affords with the adjacent nitrile function quinazoline derivatives **256** (91JHC1857).

A recently developed synthesis (Scheme 94) of pyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidines starts with the appropriate iminophosphorane **257**, which affords with heterocumulenes the tricyclic pyrimidines **258a-c** (94T6705).

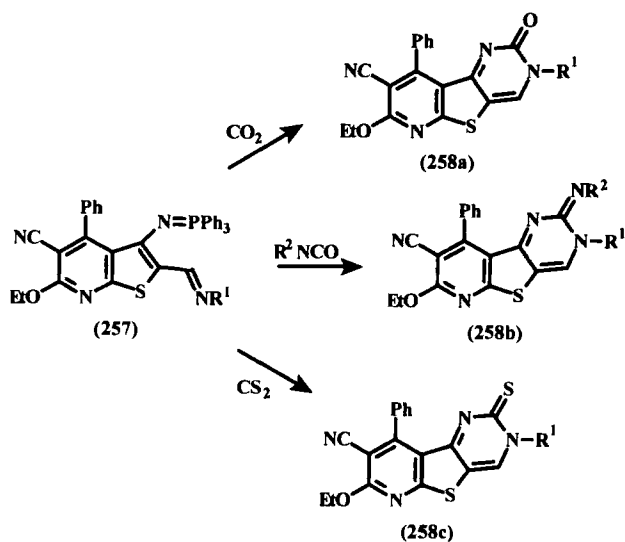


SCHEME 92

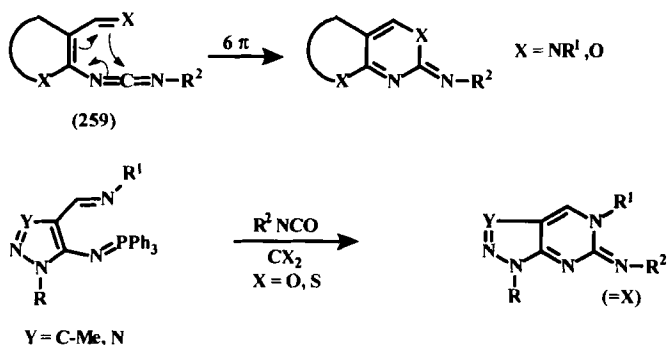


SCHEME 93

The tandem aza-Wittig/ 6π -electrocyclization strategy (94S1197) can also be applied to 1,5-diaza- or 1-oxa-5-aza-1,3,5-trienes (**259**), as shown in Scheme 95. One of the double bonds is part of the heterocyclic system, and once again, a pyrimidine ring can be condensed to an existing heterocyclic moiety (88JOC4654; 90T7855).



SCHEME 94

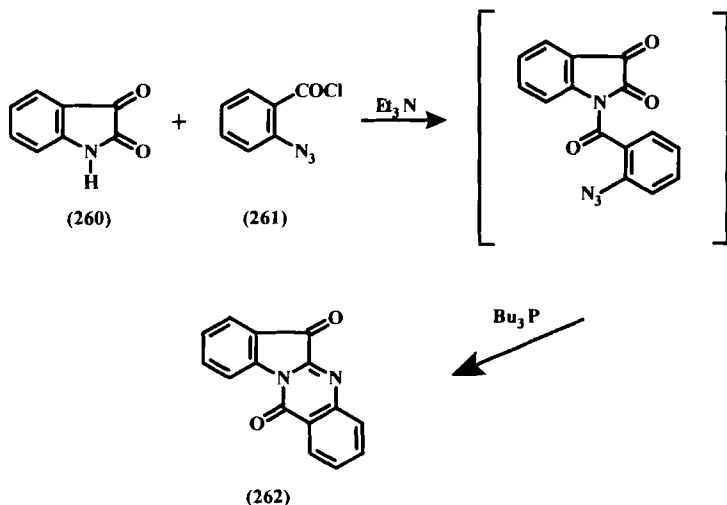


SCHEME 95

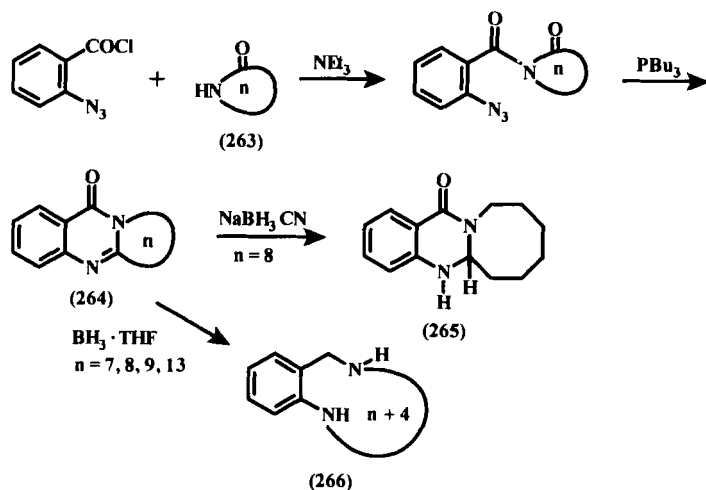
6. Quinazolines

The pharmacologically important tryptanthrine, a quinazoline alkaloid, is known for its antimycotic activity and is used against skin infections. This alkaloid is obtained from isatin (**260**) and *o*-azidobenzoyl chloride (**261**), as shown in Scheme 96. The adduct formed is cyclized via a Staudinger and an aza-Wittig reaction to afford tryptanthrine (**262**) (92H153).

As Scheme 97 shows, employing macrocyclic lactams **263** and *o*-azidobenzoyl chloride, 4(3*H*)-quinazolinones (**264**) are obtained with the aid of an aza-Wittig strategy. Reductive cleavage of the C-2 – N-3 bond of quinazo-



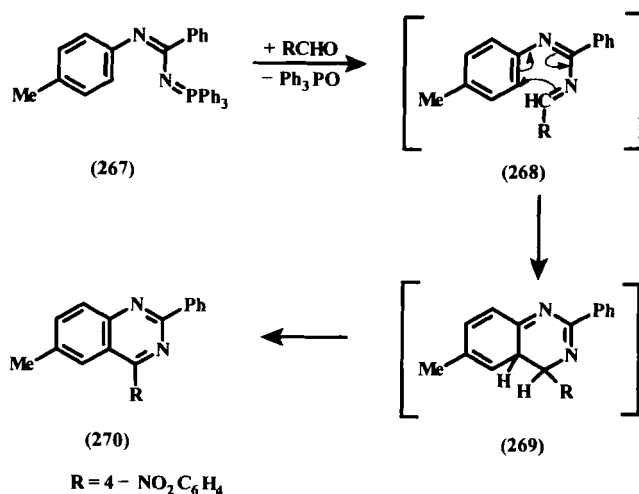
SCHEME 96



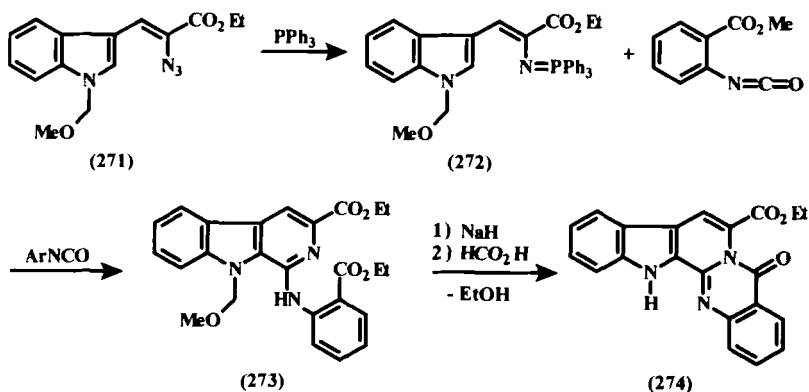
SCHEME 97

line **264** with boranes yields macrocyclic 1,5-diamines **265**. Sodium cyanoborohydride, however, reduces only the $\text{C}=\text{N}$ double bond in **264** to give **266** (91JOC1535; 92JOC6975).

Rossi *et al.* have used the tandem aza-Wittig principle (88TL3849; 89T4263; 91T5819, 91TL5379; 92JOC6703, 92T4601) in the synthesis of quinazolines (Scheme 98). In the primary step, iminophosphorane **267** is



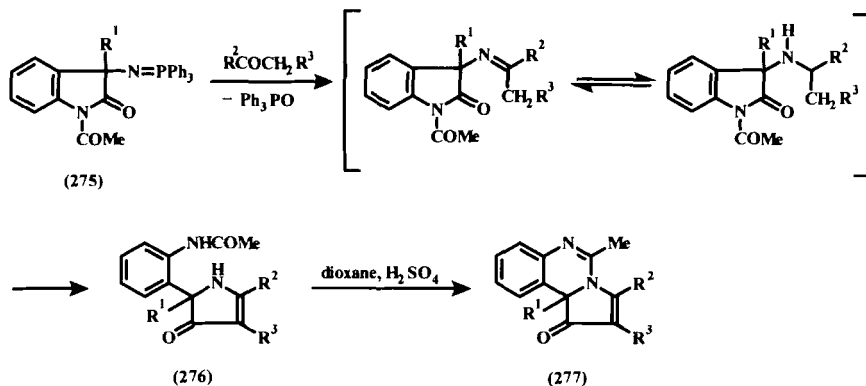
SCHEME 98



SCHEME 99

transformed with aromatic or aliphatic aldehydes into 1,3-diazabuta-1,3-dienes (**268**). A subsequent [1,3]-sigmatropic shift results in the formation of 3,4-dihydroquinazolines (**269**), which can be smoothly oxidized to quinazolines (**270**). Using other R substituents instead of 4-nitrophenyl leads to side products (91T5819).

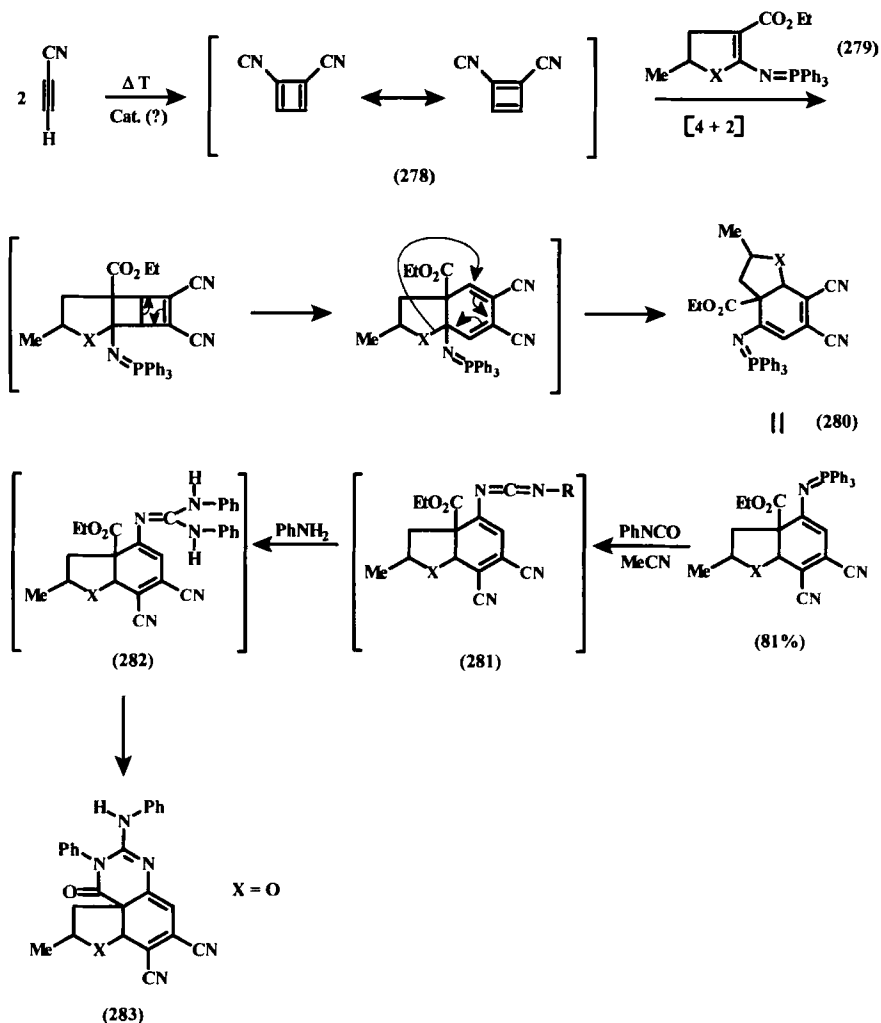
Following this general strategy, 1-methoxymethylindole-3-carbaldehydes are converted into vinyl azides **271**, which undergo a Staudinger reaction with triphenylphosphine to iminophosphoranes **272** (Scheme 99). Methyl 2-isocyanatobenzoic ester reacts via an aza-Wittig reaction to give the 1-amino- β -carboline **273** in 89% yield. Treatment with sodium hydride initiates an intramolecular cyclization of the pyridine N with the neighboring ester function to afford the pentacyclic quinoxaline **274** in 58% yield. De-



SCHEME 100

protection of the indole N atom leads to ethyl 7,8-dihydrorutecarpine-7-carboxylate, a derivative of the natural product rutecarpine which is isolated from *Evodia rutaecarpa* [93JCR(S)24].

Additional communications deal with the synthesis of pyrrolo[1,2-*c*]quinazolines by treatment of methyl 3-alkyl-1,3-dihydro-2-oxo-3-(triphenylphosphoranylideneamino)-2*H*-indole-1-carboxylates (**275**) with ketones to afford Δ^2 -pyrrolin-4-ones (**276**). As Scheme 100 shows, **276** can



SCHEME 101

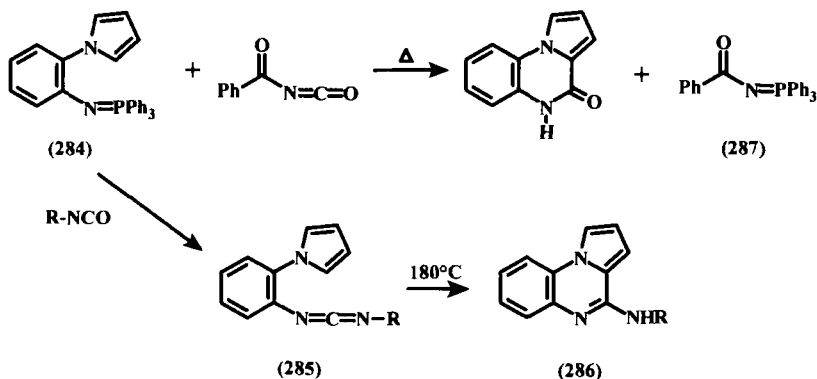
be cyclized by refluxing in dioxane containing catalytic amounts of sulfuric acid to give pyrrolo[1,2-*c*]quinazolin-1-ones (**277**) (92T5359).

A novel ring system of furo[3,2-*e*]quinazolines (**283**) was formed by the reaction with tetrahydrobenzo[*b*]furan (**280**) and aryl isocyanate (see Scheme 101). The resulting carbodiimide **281** was spontaneously transformed by addition of phenylamine into the guanidine **282**. The reason for the addition of another nitrogen onto the carbodiimide carbon is the high reactivity in the double-bonded system. In the presence of a primary amine, the guanidine intermediates cyclize to give the furo[3,2-*e*]quinazolines (**283**) (88CB2157; 86CB2723; 91MI3). Starting material **280** was accessible via a [4 + 2]-cycloaddition of the heterocyclic β -enamino ester (**279**) and the presumably elusive 1,2-dicyanocyclobutadiene (**278**), which is probably formed by a head-to-head dimerization (91MI1).

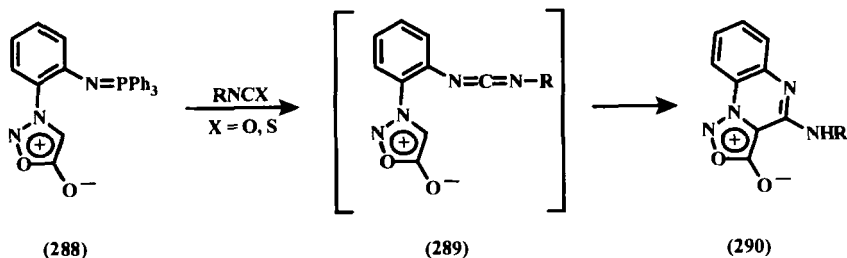
Another general route to 5,10-dihydro[1,2,4]triazolo[5,1-*b*]quinazolines via the electrocyclization of an azino carbodiimide intermediate has been described (94S1057). The key iminophosphorane, a benzophenone-1-[(triphenylphosphoranylidene)amino]ethylidenehydrazone, was easily prepared in a Kirsanov-variant first applied by Bayless and Zimmer (68TL3811). It consists of the reaction of triphenylphosphine/iodine/triethylamine with benzophenone 1-aminoethylidenehydrazone (94S1057).

7. Quinoxalines

The synthetic route to pyrroloquinoxalines **286** (Scheme 102) starts with *N*-phenylpyrrole (**284**). With isocyanate **284** affords via an aza-Wittig reaction the isolable carbodiimide (**285**), which is converted in turn by pyrolysis into the final product **286**. Treatment of **284** with benzoyl isocyanate gives



SCHEME 102



SCHEME 103

a related pyrroloquinoxaline by extrusion of benzoyliminophosphorane (287) (89TL2847; 90T1063).

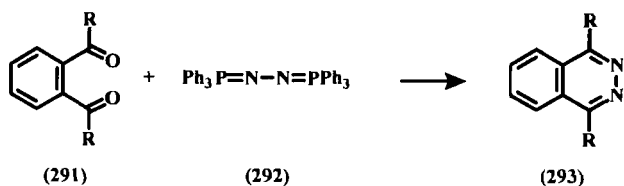
An interesting variation of this quinoxaline synthesis is outlined by the synthesis of syndnoquinoxalines shown in Scheme 103. The starting material is phenylsydnone **288** with an iminophosphorane group in an *o*-position. With isocyanate or isothiocyanate carbodiimide intermediates **289** are formed; by an electrophilic aromatic substitution at the sydnone ring (4 position), the 4-(arylamino)syndno[3,4-*a*]quinoxalines (**290**) are obtained (91S745).

8. Phthalazines

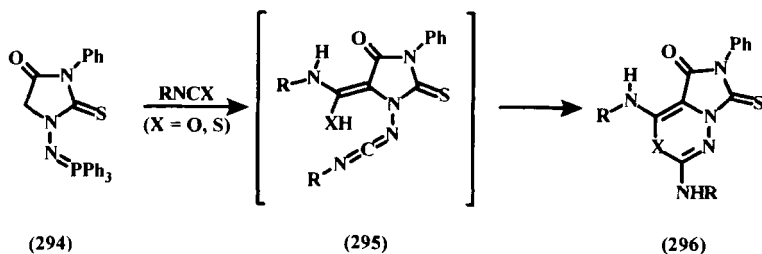
Bisiminophosphorane (**292**) affords phthalazines **293** by a twofold aza-Wittig reaction with phthalaldehydes, as shown in Scheme 104. 1,2-Diacylbenzene derivatives can be employed as well (68MI1).

9. 1,3,4-Oxadiazines and 1,3,4-Thiadiazines

The synthetic route to 1,3,4-oxadiazines and 1,3,4-thiadiazines (Scheme 105) begins with the iminophosphorane of imidazolone **294**, which is converted with isocyanate or isothiocyanate to carbodiimide **295**. A second addition of the heterocumulenes occurs to the CH acid at the 5-position,



SCHEME 104



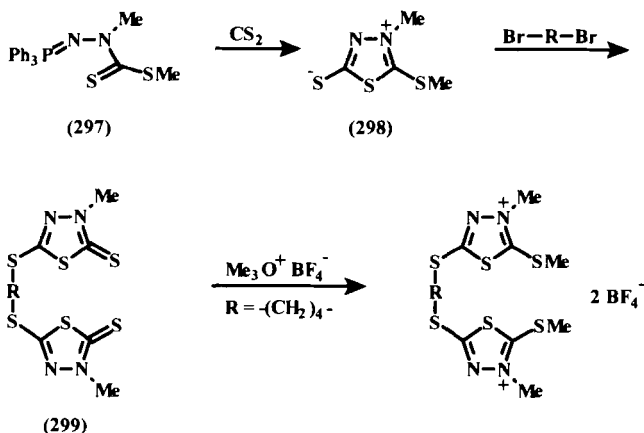
SCHEME 105

forming an internal nucleophile which is then intercepted by the carbo-diimide with cyclization to **296** (90T4353).

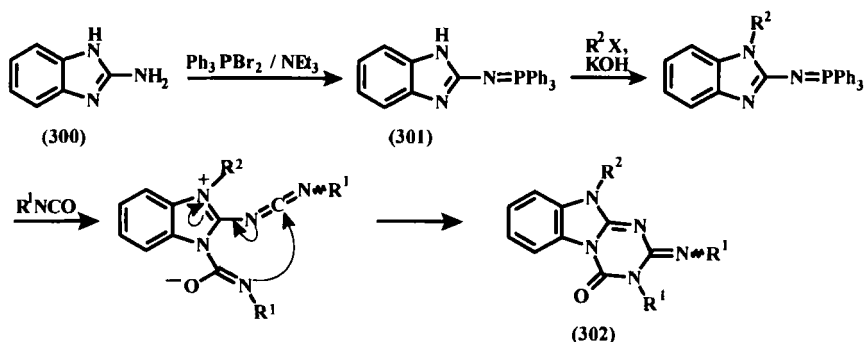
Molina *et al.* were able to prepare the mesoionic thiadiazole (**292**) from iminophosphorane **297** and carbon disulfide. As Scheme 106 shows, **298** reacts with α,ω -dihalo compounds to form dimer **299** [91JCS(P1)1159]. The synthesis of the mesoionic thiazolo[2,3-*b*][1,3,4]thiadizole is described in (92T1285).

10. 1,2,4-Triazines and 1,3,5-Triazines

Triazines now are widely used as pesticides. Scheme 107 shows one approach to this class of compounds, which consists in the conversion of the iminophosphorane of 2-aminobenzimidazole (**301**). After alkylation of the benzimidazole ring, treatment with two equivalents of isothiocyanate affords cyclization to 1,3,5-triazino[1,2-*a*]benzimidazole (**302**) (92S297).



SCHEME 106

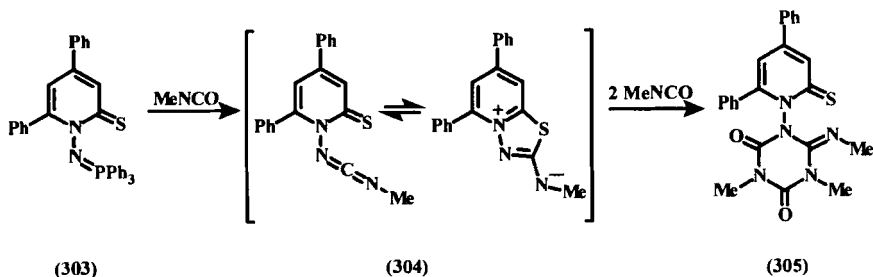


SCHEME 107

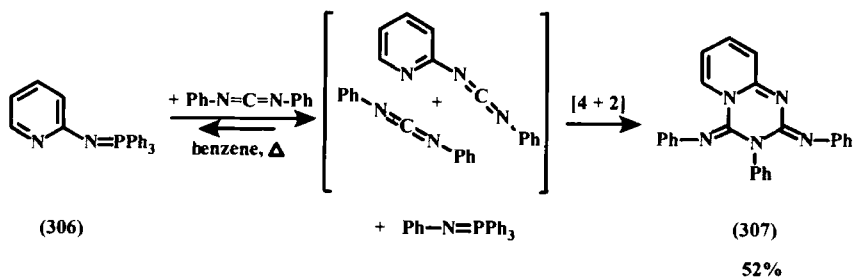
In another approach (Scheme 108), phosphorylated 1-amino-2-pyridinethione (**303**) gives carbodiimide (**304**) with methyl isocyanate; **304** in turn undergoes a [2 + 2 + 2]-cycloaddition to 1,3,5-triazine (**305**) (88-CB1495).

The synthetic route to pyrido[1,2-*a*][1,3,5]triazines (**307**) is exemplified by reacting *N*-(2-pyridyl)iminophosphorane (**306**) and diphenylcarbodiimide. This reversible transamination to a mixed carbodiimide is shown in Scheme 109. Excess diphenylcarbodiimide function as a reaction partner, as dimerization seems to be sterically hindered (77ZC371).

However, when pyridyliminophosphorane (**306a**) is treated with phenyl isocyanate or isothiocyanate (Scheme 110), mixed carbodiimides are obtained, which are capable of an intermolecular Diels–Alder reaction resulting in triazine **308**. The cycloaddition occurs specifically with one C=N double bond of the carbodiimide serving as the dienophile (77ZC371).



SCHEME 108



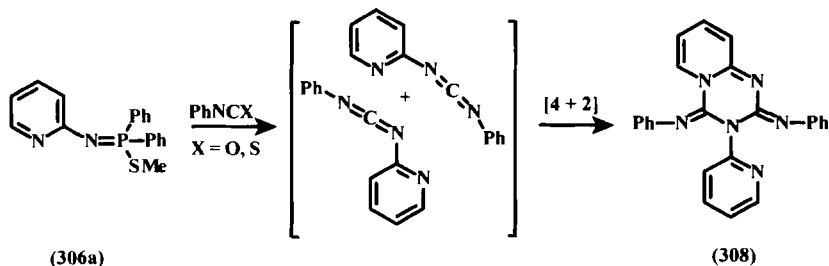
SCHEME 109

Starting from 1-amino-2-methylthio-4-phenylimidazole, a double aza-Wittig reaction (Scheme 111) furnishes the imidazo[1,2,4]triazine (**309**) (89S843).

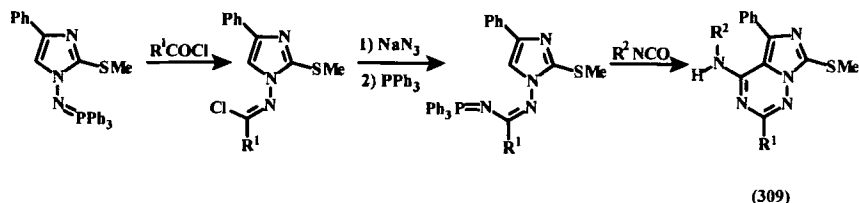
The aza-Wittig reaction (Scheme 112) of the iminophosphorane of 1,2,4-triazine (**310**) and several isocyanates affords 1,3,4-thiadiazolo[2,3-c][1,2,4]triazinium-7-imide (**311**) possessing a mesoionic structure (91T-6747; 94S1197).

11. 1,2,4,5-Tetrazines

These colorful heterocycles, also named *s*-tetrazines, have been of increasing interest due to their biological activity (herbicides) (78HC1073). A simple one-pot synthesis of symmetric 3,6-disubstituted *s*-tetrazines (Scheme 113) has been developed by Wamhoff *et al.* Dichlorotriphenylphosphorane formed *in situ* converted aroylhydrazines (**312**) into dihydrotetrazines (**314**) via iminophosphorane intermediates (**313**) in a head-to-tail 1:1 aza-Wittig reaction. These dihydrotetrazines are smoothly oxidized (NBS, O₂ etc.) to afford *s*-tetrazines (**315**) in high yield (80CB2566). Mild reaction conditions and a broad range of substituents (aryl, alkyl, 4-pyridyl, 2-thienyl, 2-furyl) characterize the advantages and general applicability of this synthesis.



SCHEME 110



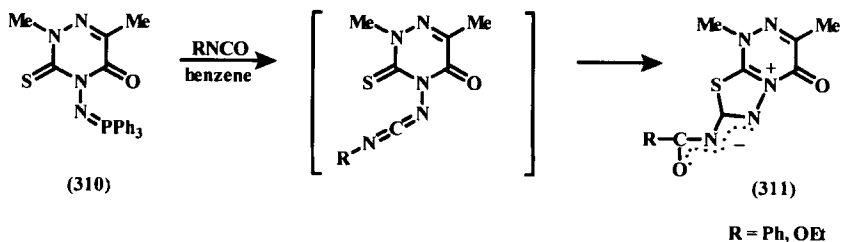
SCHEME 111

Related to this principle is the reaction of benzoylhydrazide with dibromotriphenylphosphorane and triethylamine to give 3,6-diphenyl-1,2,4,5-tetrazine via *N*-(benzoylamino)aminophosphonium salts (68JA5626). With the aid of an aza-Wittig reaction a tetrahydro-1,2,4,5-tetrazine ring can be annulated to an existing 1,2,4-triazine ring by employing iminophosphorane **316**, which forms the corresponding hydrazine **317** with acid chlorides (Scheme 114). Thermal cyclization then leads to the 1,4-dihydro-1,2,4-triazino[4,3-*b*][1,2,4,5]tetrazine (**318**) (88T2249).

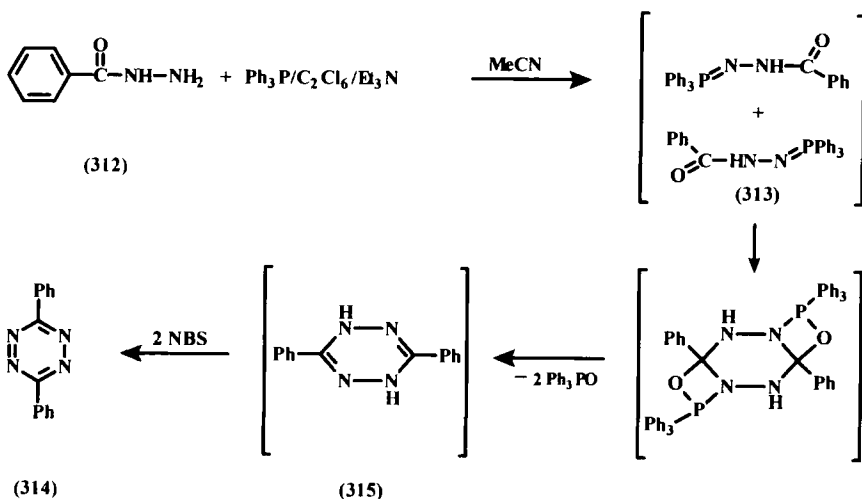
E. SEVEN-MEMBERED HETEROCYCLES

1. Azepines and Derivatives

The simplest examples of this series containing one nitrogen-atom as part of a seven-membered ring are cyclic imines (**320**), which are available by intramolecular aza-Wittig cyclization of ϵ -azido ketones (**319**) by treatment with triphenylphosphine, as shown in Scheme 115 (82CC1224). This general principle can also be applied to bicyclic azido ketones, which are capable of forming a seven-membered bridgehead imine, as well as to β -dicarbonyl compounds (83JA5912; 87H3265).



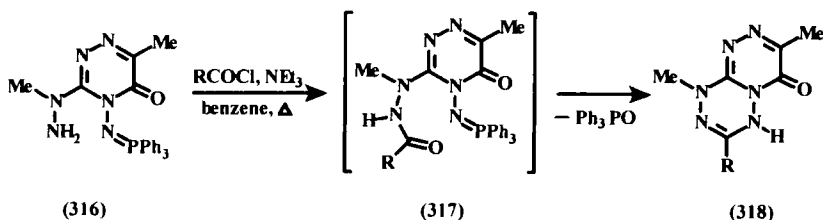
SCHEME 112



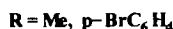
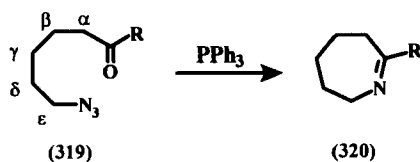
SCHEME 113

However, dicarboxylic acid dichlorides treated with iminophosphoranes (Scheme 116) show a substrate-dependent reaction. Thus, *o*-benzodiacetyl dichlorides (**321**) form chloroazepinones (**322**) only with *N*-aryliminophosphoranes. *N*-Alkyliminophosphoranes, upon elimination of dichlorotriphenylphosphorane and subsequent Mumm rearrangement (71M168), give the cyclic imide (**323**) (90S149; 91T53).

7-Chloroazepin-2-ones are obtained via adipic dichloride (**324**) or *o*-benzodiacetyl dichloride and iminophosphorane (Scheme 117). Intramolecular aza-Wittig reaction forms the imidoyl chloride, which can be attacked nucleophilically by the carbonyl oxygen of a second acid halide. The resulting carbocation stabilizes itself by deprotonation to form the cyclic imino ester, which undergoes a Chapman rearrangement to give chloroazepinone **325** (90S149; 91T53).



SCHEME 114



SCHEME 115

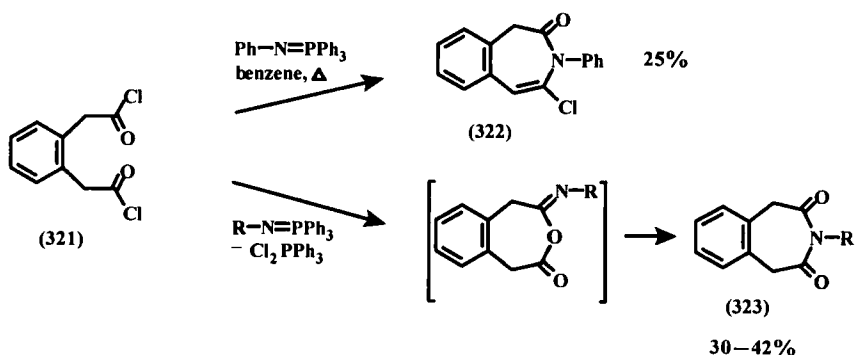
2. Benzazepines

As shown for the aziridines, BETMIP (**68**) has proved to be useful in the synthesis of azepines (Scheme 118). Treatment with methylenephosphorane leads to a phosphonium salt which in turn is deprotonated with BuLi and cyclized with benzene-1,2-dialdehyde in a Wittig and aza-Wittig step to form benzazepine **326** (93JOC1987).

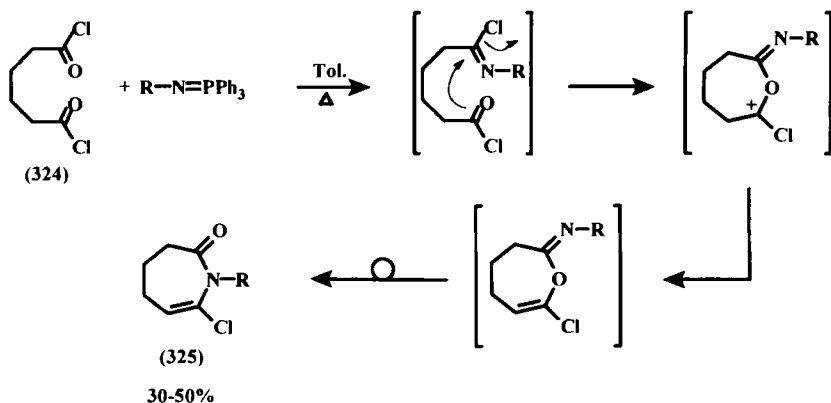
3. 1,3-Benzoxazepines

Kurita *et al.* reacted α -azidocinnamate **327** with benzoyl chloride (Scheme 119) to form benzoate **328**, which upon conversion of the azide group into an iminophosphorane (**329**) underwent an aza-Wittig cyclization to yield 1,3-benzoxazepine (**330**) (92CC81).

As Scheme 120 shows, more benzoxazepines are available by aza-Wittig cyclization of *o*-acyloxy-2-azidoacetophenone (**331**). The benzoyloxy derivatives, however, eliminate triphenylphosphane oxide but afford an acyclic product (**332**) for steric reasons (90S455).



SCHEME 116



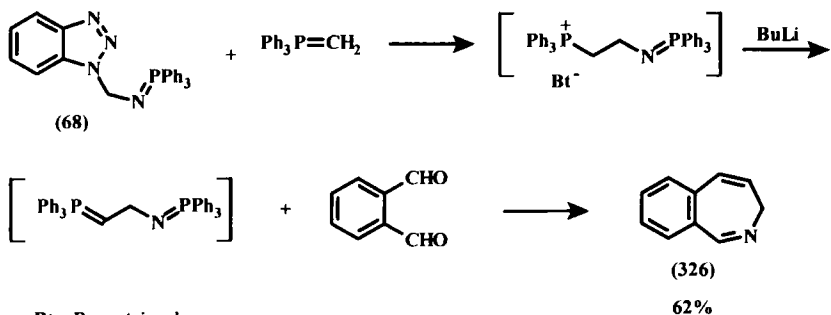
SCHEME 117

4. Benzodiazepines

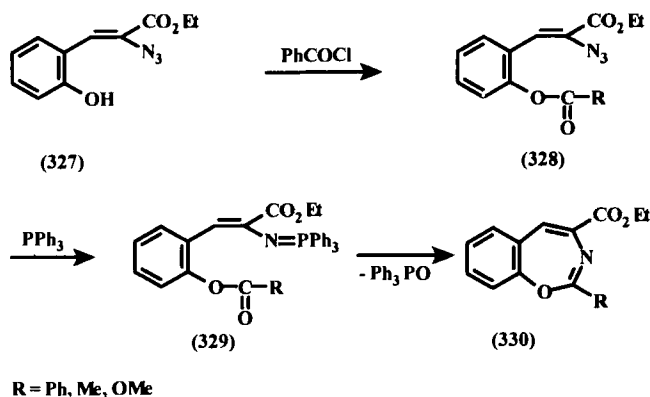
In analogy to the benzoxazepines, Kurita *et al.* have also synthesized 1,3-benzodiazepines (91TL4401) from *o*-acylamino- α -azidocinnamates (92CC81).

1,4-Diazepines represent an important class of bicyclic seven-membered heterocycles. They are the basis of several tranquilizers and are accessible from α -amino acid esters and *o*-azidobenzoyl chloride in the presence of triethylamine. The *N*-(*o*-azidobenzoyl)amino esters (**333**) formed in this way (Scheme 121) are cyclized by Staudinger and aza-Wittig reactions to give 2-ethoxy-1,4-benzodiazepin-5-ones (**334**) (92MI2).

Via tandem Michael-type addition followed by an aza-Wittig reaction, 2,3,6,7-tetrahydro- and 2,3,4,5,6,7-hexahydro-1*H*-1,4-diazepines have



SCHEME 118



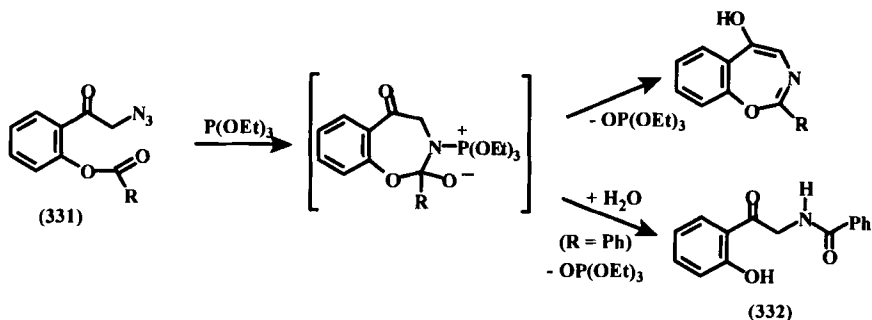
SCHEME 119

been prepared (Scheme 122). The conversion of tetrahydro- (336) into hexahydrodiazepine (337) is effected by lithium aluminium hydride [93JCS(P1)1061].

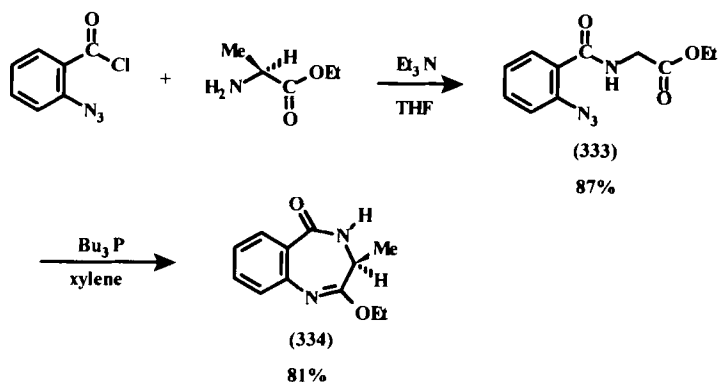
5. Benzotriazepines

The iminophosphoranes of methyl arylhydrazono acetates (338) possessing a keto function in an *o*-position afford 1H-1,2,4-benzotriazepines (339) upon heating (Scheme 123). The yield depends on the substituents and solvents employed. Methoxycarbonyl-, 4-pyridyl-, and 3-pyridyl groups activate the carbonyl function and improve the yield. Reactions of alkyl ketones and aldehydes proved to be unsuccessful [91JCR(S)2].

The tandem aza-Wittig/6 π -electrocyclization principle has been used for the synthesis of 1,3,5-benzotriazepines. After pioneering work done by

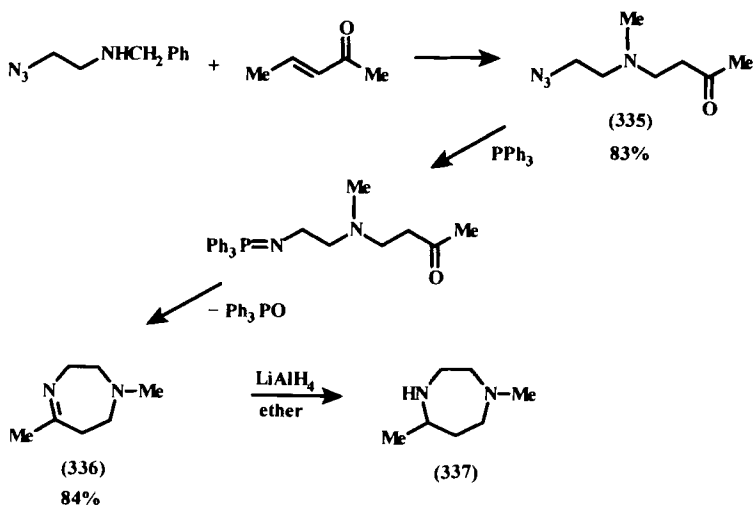


SCHEME 120

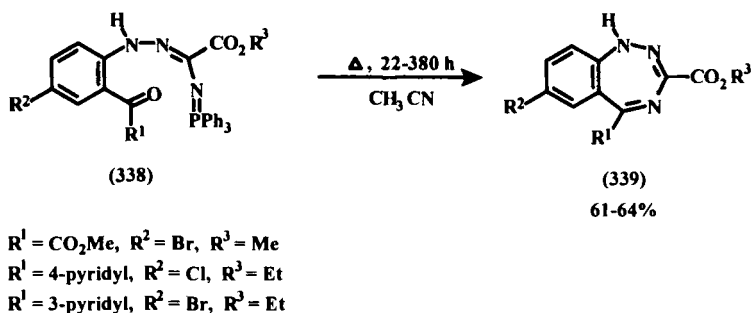


SCHEME 121

Saito *et al.*, this principle was then applied by Molina and his group to a broad range of molecules (94S1197). Thus, diazide **340** was transformed via a Staudinger reaction to bisiminophosphorane **341** with partial cyclization to 1*H*-1,2,4-triazolo indazole (Scheme 124). Treatment with ethyl isocyanate leads to a pentacyclic 1,3,5-benzotriazepine (**343**) in 52% yield. With other isothiocyanates the yield can be improved to 82% (91TL2979; 92T3091; 94S1197).

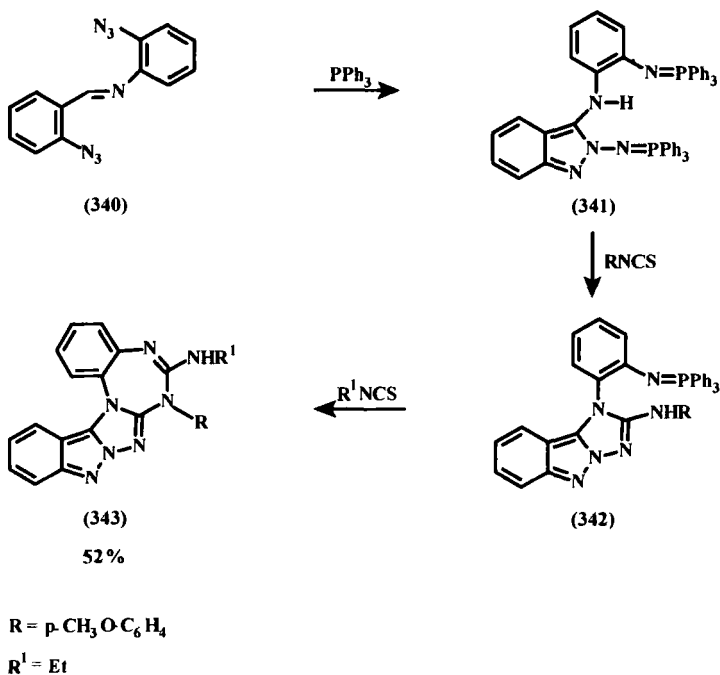


SCHEME 122

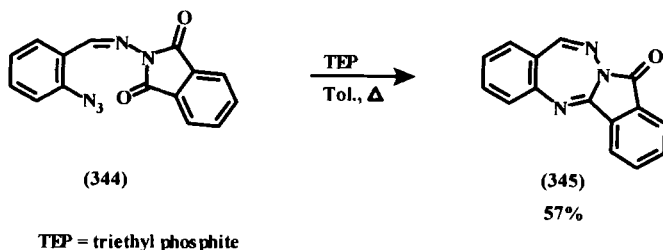


SCHEME 123

Another variant (Scheme 125) is represented by the synthesis of isoindolo-1,3,4-benzotriazepinones (**345**). The starting material can easily be obtained from *o*-azidobenzaldehyde and *N*-aminophthalimide. Subsequent aza-Wittig reaction converts **344** to the tetracyclic 1,3,4-benzotriazepinone (90TL6561).



SCHEME 124



SCHEME 125

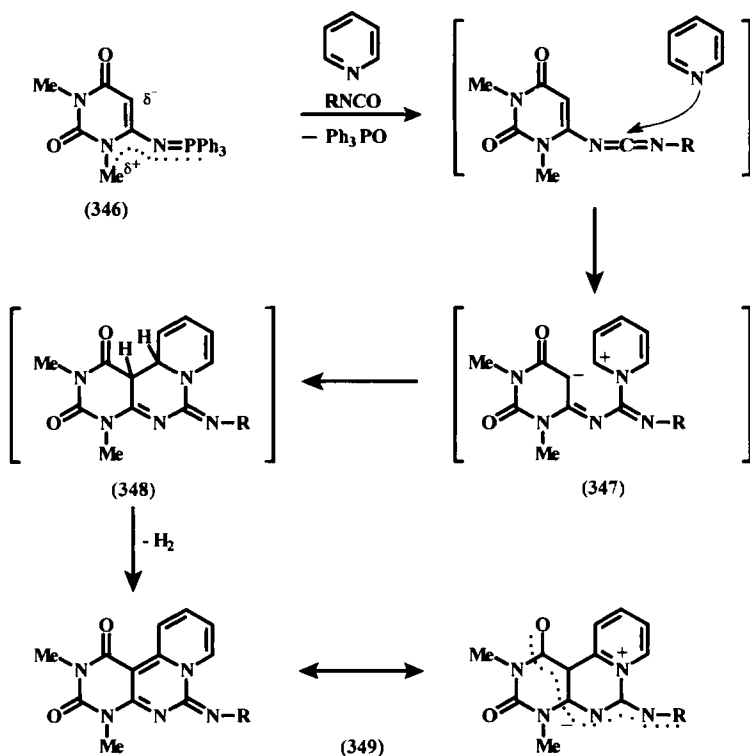
VII. Iminophosphoranes as Versatile Starting Materials in the Three-Component Reaction: Iminophosphorane-Heterocumulene-Heteroarene

This last section underlines once again the great synthetic potential of the iminophosphorane group, as predicted by Staudinger and Meyer after their first successful synthesis of the $P=N$ double bond. Recently, iminophosphoranes have proved to be novel and versatile heteroannulation components in their reaction with two other components: heterocumulenes and heteroarenes ($C=X$ double bonds).

The broad applicability follows from the fact that both the heterocumulene and the heteroarene ($C=X$ double bond) can be varied widely. Uracils, pyrazoles, pyrazolones, and carbocycles can be chosen as heterocyclic iminophosphoranes; suitable heteroarenes ($C=X$ double bonds) include pyridines, pyridine alkaloids, quinolines, isoquinolines, lactim ethers, imines, azo compounds, and 1,2,4-triazoline-3,5-diones. As heteroannulenes, a broad choice of isocyanates, isothiocyanates, ketenes, CO_2 , CS_2 , etc., can be applied. The major advantage of this reaction is the straightforward synthesis of novel zwitterionic oligoheterocyclic systems. A somewhat related approach by Molina *et al.* (92T1285; 94S1197) employs tandem azo-Wittig/ 6π -electron cyclization to afford higher yields. However, the intermediate for intramolecular cyclization requires a preceding multistep approach.

A. HETEROCONDENSED URACIL BETAINES

In a one-pot reaction (Scheme 126) the iminophosphorane of 6-aminouracil (**346**) (92AHC129) is transformed with isocyanate in the presence of pyridine into a nonisolable carbodiimide. Spontaneous addition of pyridine follows to give a 1,6-dipolar pyridinium ylide (**347**), which cyclizes to the



R = phenyl

R = 4-nitrophenyl

R = isopropyl

R = 4-(methylphenyl)sulfonyl

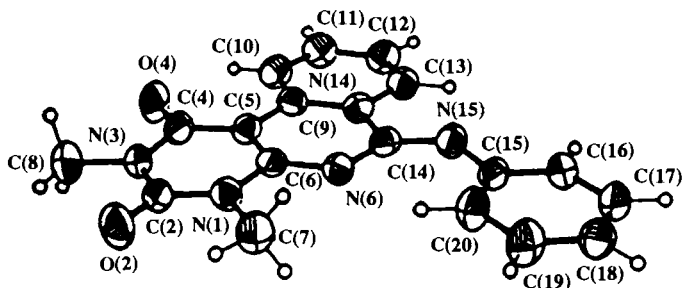
R = cyclohexyl

R = 4-chlorophenyl

SCHEME 126

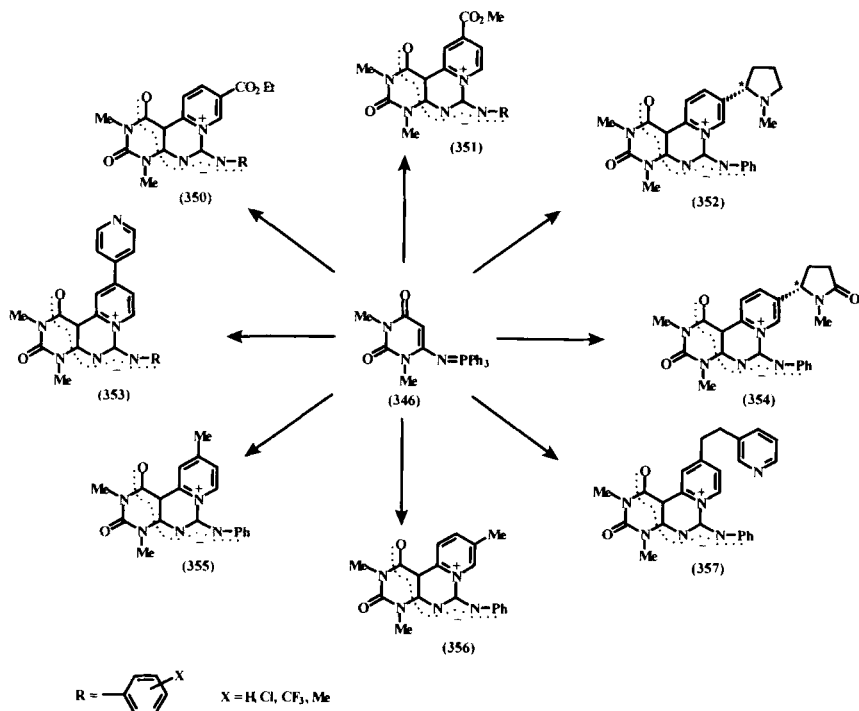
tricyclic intermediate **348**. Dehydrogenation affords the novel pyrido-[1,2-*f*]pyrimido[4,5-*d*]pyrimidine (**349**) (91TL4473; 93JOC6976).

In analogy to the studies by Potts *et al.* (88JOC2889, 88JOC2898) on cross- and pseudocross-conjugated mesoionic betaines, zwitterionic forms are postulated for **349**, whose ORTEP presentation (91TL4473) is given in Scheme 127. Thus, the C-5—C-9 bond of **349** (R = C₆H₅) shows σ and π character, having a length of 142.2 pm. The bond distance between C-14 and N-14 is significantly increased (147.5 pm) and does not allow any π overlap between C-14 and the pyridine ring.



SCHEME 127. ORTEP presentation of (349) (91TL4473).

With increasing polarity of the solvent, the UV-absorption maxima are significantly hypsochromically shifted. This marked negative solvatochromism is considered to be an unequivocal indication of charge separation in the ground-state molecule (58JA3253; 59JA856; 66TL3369; 69AG195; 79AG119; 93PAC2593). This is explained by HOMO–LUMO excitation



SCHEME 128

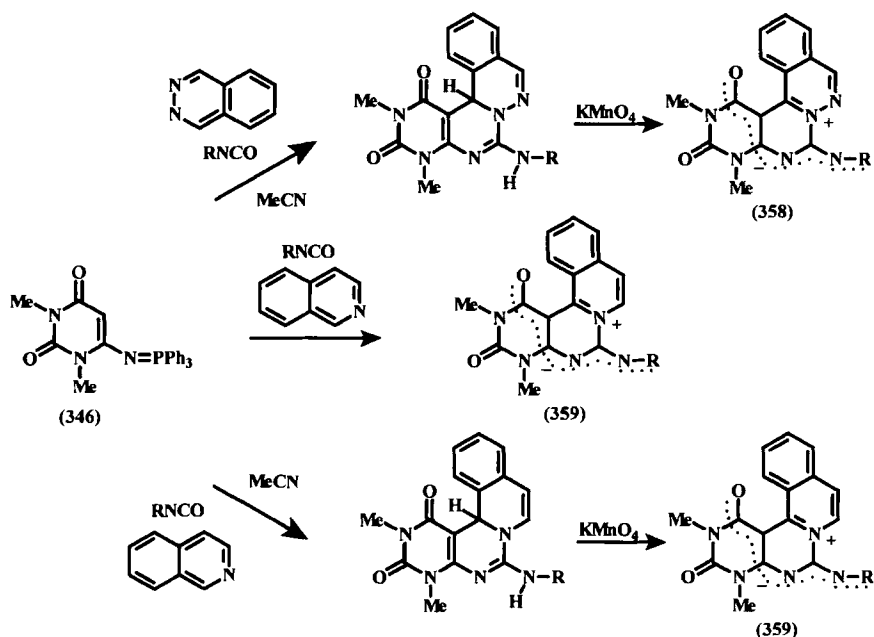
and be charge-transfer conversion, which is facilitated by less polar solvents and hence impeded by strong polar solvents (76LA1953; 79AG119; 93PAC2593).

^1H -NMR spectra show lowfield shifts of H-8, H-9, and H-11 caused by anisotropic effects of both $\text{C}=\text{O}$ and $\text{C}=\text{N}$ groups and also by the positively charged pyridinium moiety. ^{13}C -NMR data reveal analogous effects, pointing to a charge separation between the pyridinium part and the extended negative chromophore (349).

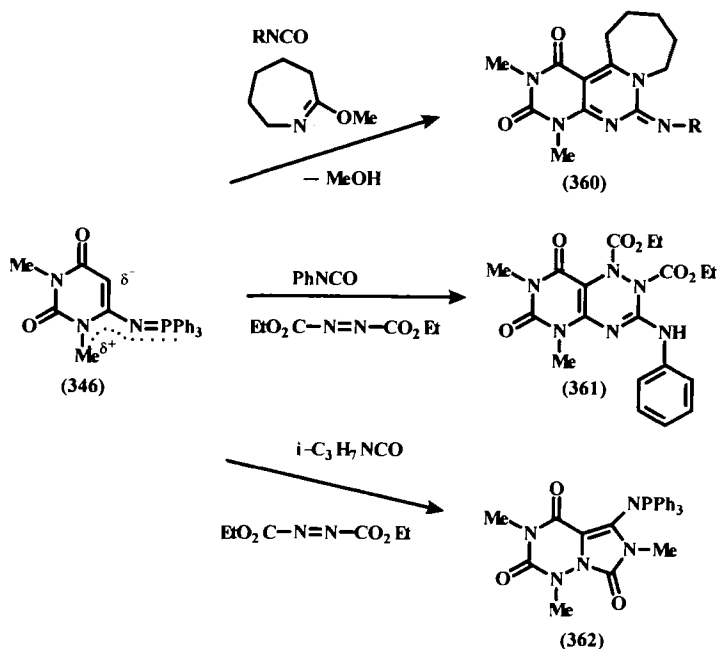
The synthesis of these zwitterions contains the following four partial steps:

- (1) aza-Wittig reaction as an initiating step to carbodiimide formation;
- (2) addition of a nucleophilic N atom of the heteroarene ($\text{C}=\text{N}$, $\text{N}=\text{N}$) to the highly electron-deficient carbodiimide C; formation of 1,6-dipolar pyridinium ylide stabilized by resonance;
- (3) cyclization to form a dihydro product;
- (4) oxidation and formation of the zwitterionic product.

Scheme 128 shows the broad range of products obtained within the pyridine series (93JOC6976).



SCHEME 129



SCHEME 130

With phthalazine as the heteroarene component and isocyanate in acetonitrile as solvent, uracil **346** affords pyrimido[4',5':4,5]pyrimido[6,1-*a*]phthalazine (**358**) in a similar way. The combination with isoquinoline affords **359** after KMnO_4 oxidation. However, with isoquinoline as solvent, **359** is directly available. (See Scheme 129).

Additionally, uracil 6-iminophosphorane, isocyanate, and *o*-methyl- ϵ -caprolactim ether join to form the intensely yellow pyrimido[4',5':4,5]pyrimido[6,1-*a*]azepine (**360**), as shown in Scheme 130. Upon ring closure, methanol is spontaneously eliminated. Diethyl azodicarboxylate affords with the other components pyrimido[4,5-*e*][1,2,4]triazoline (**361**), which is closely related to the alkaloid isofervenuline. The imidazo[5,1-*f*][1,2,4]triazine (**362**) results in a known Michael-type rearrangement sequence by treatment with diethyl acetylenedicarboxylate (86JOC149, 86JOC2787); in this latter case, the Michael-type addition occurs much faster than the expected three-component reaction [93H(35)1055].

B. ZWITTERIONIC HETEROCYCLIC PYRAZOLES

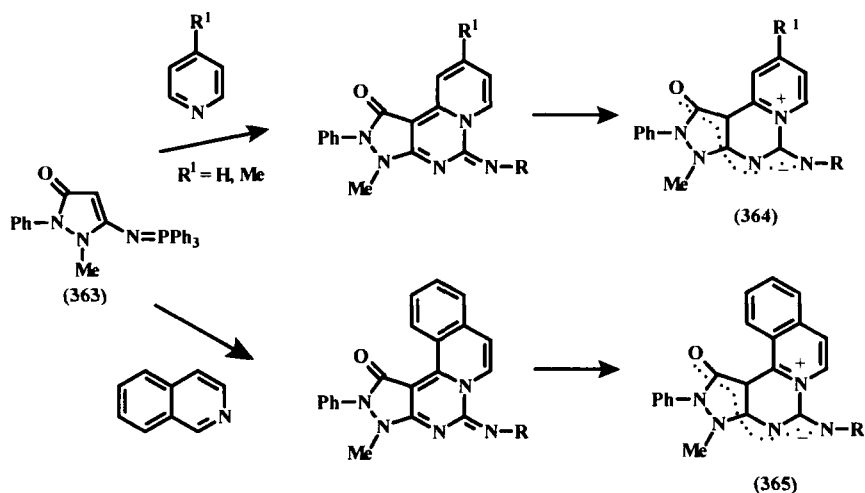
Besides uracil-6-iminophosphorane, the iminophosphorane component was extended to pyrazole **368** and pyrazolon-4-iminophosphoranes **363** (94JOC3985). In its electron distribution, **363** can be compared with uracil **346**. With arylisocyanates, pyridine, or γ -picoline, zwitterionic pyrazolo [3',4':4,5]pyrido[6,1-*a*]pyrimidines (**364**) are obtained; and with isoquinoline, **365** is formed (Scheme 131). Again, both systems show a typical negative solvatochromism (94JOC3985).

Furthermore, pyrazole **366** reacts with phthalazine (Scheme 132) to afford pyrazolo[3',4':4,5]pyrido[6,1-*a*]phthalazine (**367**). From a mechanistic viewpoint, no 1,6-dipolar cyclization occurs. Instead, an intramolecular nucleophilic aromatic substitution to the heteroarene is likely. Isoquinoline leads to zwitterionic **368** (94JOC3985).

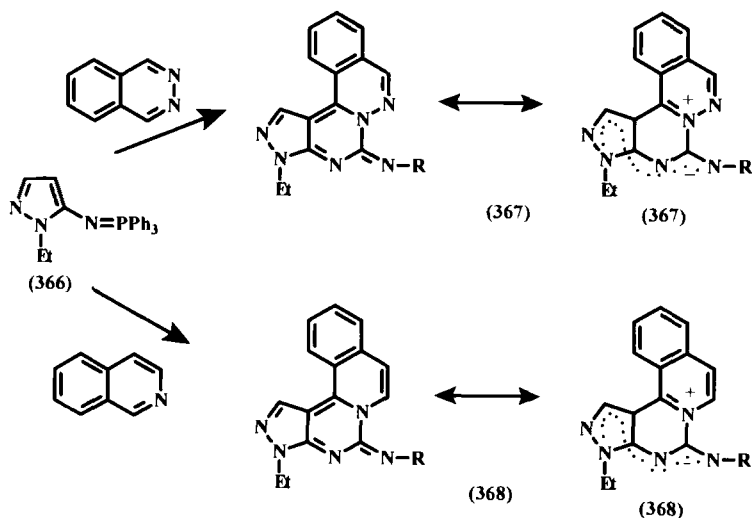
Compilation of the results obtained up to now shows that the aromaticity of the iminophosphoranes plays a minor role, while the aromaticity of the heteroarenes is strongly influential. These observations have been supported by spectroscopic data.

C. SCOPE AND LIMITATIONS OF THE THREE-COMPONENT REACTION

After UV irradiation, betaine **369** exhibits a novel "photooxidative inter-conversion," as shown in Scheme 133. The originally deep red starting



SCHEME 131

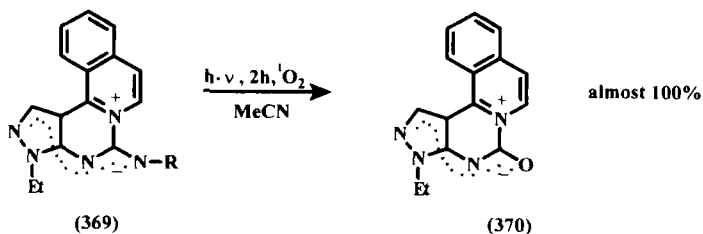


SCHEME 132

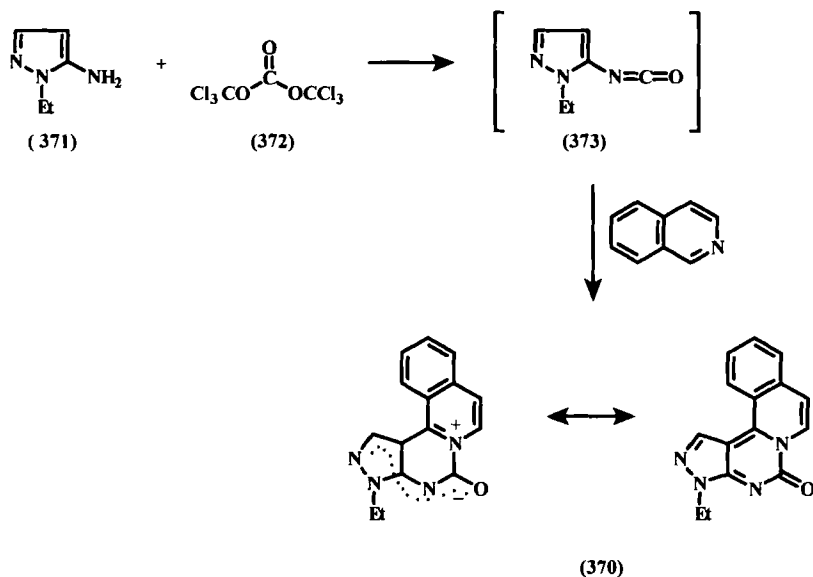
material was transformed into an intensely yellow-green fluorescent compound **370** in almost 100% yield. The mechanism of this reaction has not yet been studied in detail; however, a mechanism involving a 1,2,3-dioxazetidine route by cycloaddition of singlet oxygen has been suggested (94UP1).

Compound **370** can also be obtained by direct cycloaddition of the isoquinoline to the pyrazole isocyanate (**373**), which is generated *in situ* from the corresponding amine **371** and (bischloromethyl)carbonate **372** (Scheme 134) (94UP1).

Betaines **375** and **376** could be isolated in the three-component reaction of carboxylic iminophosphoranes (**374**) with aryl isocyanates and pyridines or quinolines as heteroarene components (93UP1). This route (Scheme 135) opens another broad range of novel heterocyclic systems.

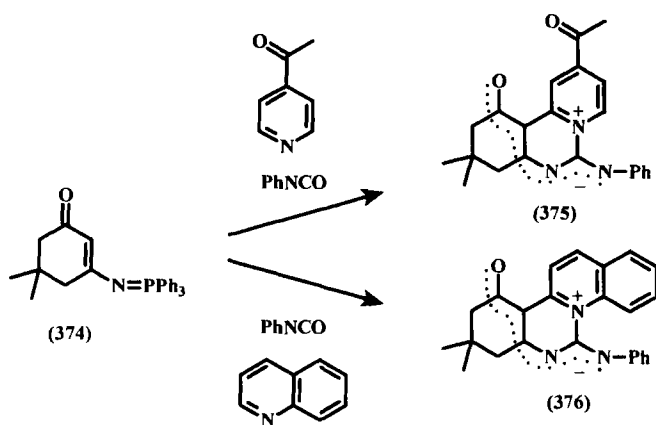


SCHEME 133



SCHEME 134

The three-component reaction with ketene as the heterocumulene component and 6-aminouracil (Scheme 136) leads to both zwitterionic heteropolycyclic uracils and their monohydro products. For example, **377** is obtained by treatment of diphenylketene and pyridine in a 42% yield. However, diphenylketene and quinoline are transformed into the zwitterionic **378** in a satisfactory yield of 54% (94UP2).



SCHEME 135



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Recent Developments in Ring-Chain Tautomerism

I. Intramolecular Reversible Addition Reactions to the C=O Group*

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I. Introduction	252
A. General Considerations	252
B. Methods of Investigation	255
II. Intramolecular Reversible Addition Reactions to the C=O Group	258
A. Oxocarboxylic Acids and Derivatives Modified at the Carboxylic Group ...	258
1. Oxocarboxylic Acids	258
2. Chlorides and Azides	261
3. Amides	263
B. Hydroxy Aldehydes and Ketones and Related Compounds	268
1. Derivatives Containing a C—OH Group	268
2. Derivatives Containing a N—OH Group	285
C. Amino Aldehydes and Ketones and Related Compounds	286
1. Derivatives Containing an Amino Group on an sp^3 or Aromatic Carbon Atom	286
2. Covalent Hydration of Nitrogen-Containing Heterocycles and Heterocyclic Pseudobases	288
3. Urea, Thiourea, and Guanidine Derivatives	290
4. <i>O</i> -(3-Oxoalkyl)hydroxylamines	292
5. 3-Oxoalkylhydrazines	293

* This chapter is the first part of a review that updates an earlier work by R. E. Valters and W. Flitsch, *Ring-Chain Tautomerism* (A. R. Katritzky, ed.), Plenum Press, New York and London, 1985. The second part of this review, to be published in a subsequent volume of *Advances in Heterocyclic Chemistry*, includes data (1982–1993) for intramolecular reversible addition reactions to C=N, C≡N, C=C, and C≡C groups.

6. Monohydrazones of 1,3-Diketones and Related Compounds	294
7. Hydroxytriazine Derivatives	306
D. Addition of a SH Group	307
E. Intramolecular Acyl Group Migration	308
F. Cyclols	309
References	311

I. Introduction

A. GENERAL CONSIDERATIONS

The aim of this review article is to update an earlier book (I)¹ written by one of us (R. E. V.) together with Professor Wilhelm Flitsch. This book was the first and has remained the only detailed survey published in English on the topic of the ring-chain tautomerism of organic compounds [for the first book in Russian, see (78M11)]. In the book (I), the literature was covered up to the end of 1982. Since that time (1983–1993), many interesting and important data have been published. New types of ring-chain tautomeric systems have been described; these include systems with different interacting groups having equilibria of more than two (sometimes up to six) components with the participation of more than one open-chain and/or cyclic tautomers. The scope of spectroscopic methods for the investigation of these equilibria has been broadened considerably. Investigations (87JOC3821; 91T4031; 93JOC1967, 93T2115) have been reported that allow a quantitative evaluation of the influence of the connecting-link structure and of the electronic and steric effects of substituents on the state of the ring-chain tautomeric equilibria in a large pool of compounds.

Ring-chain tautomeric interconversions of organic compounds can be divided into two groups. The first group deals with interconversions in which an open-chain system forms a cyclic system (or vice versa) by means of electron rearrangement without the migration of atoms or functional groups. Generally called valence isomerism [76AHC(S)1], these interconversions are not discussed either in the book (I) or in this article.

In the second group of ring-chain tautomeric interconversions, an open-chain system is transformed into a cyclic system through the intramolecular reversible addition of a functional group to a polar multiple bond **1A** \rightleftharpoons **1B**; **2A** \rightleftharpoons **2B**; **3A** \rightleftharpoons **3B**; and **4A** \rightleftharpoons **4B**. The book (I) and this article deal with

¹ Here and below, "book (I)" refers to the book by R. E. Valters and W. Flitsch, *Ring-Chain Tautomerism* (A. R. Katritzky, ed.), Plenum Press, New York and London, 1985; and references such as "(I-29)" indicate the page number therein.



this type of ring-chain tautomerism. Here, the letter **A** refers to the open-chain tautomers, and the letter **B** to the cyclic forms. When there are a number of open chain and/or cyclic tautomers in the equilibrium, the letters **A**, **A'**, **A''** and **B**, **B'**, **C**, **D** are used. The fragment of a molecule connecting the two mutually reacting functional groups is designated by a semicircle.

The process of the interconversion of an open-chain tautomer into a cyclic form formally involves three stages: (1) Q-X bond cleavage, (2) Q-Y or Q-Z bond formation (ring closure), and (3) Z-X or Y-X bond formation. The sequence of these stages may vary. Most commonly, the migrating particle X is a proton.

Numerous polar multiple bonds Y=Z or $\text{Y}\equiv\text{Z}$, such as C=O , C=N , C=S , $\text{C}\equiv\text{N}$, C=C , etc., and a large number of functional groups Q-X ,

such as $O-H$, $N-H$, $S-H$, $C(O)-Hal$, etc., are capable of intramolecular addition to these bonds. The connecting fragment of the molecule, designated by a semicircle, can also possess various structures. However, it is subject to one important condition for reversible intramolecular addition-elimination reactions to occur: it must ensure a favorable steric disposition of the interacting functional groups $Q-X$ and $Y=Z$ ($Y \equiv Z$).

The organization of the material in this review is the same as that in (I). The literature reviewed covers the period 1982-1993. Papers published earlier are cited only when a more detailed explanation of the background of the problem is necessary. The first systematic review on this topic was presented by Jones (63CRV461).

During the past decade, review articles [82UK1374; 84MI1; 85APO(21)37; 86APO(22)1; 88KGS3; 92KGS851; 93ACR476, 93KGS991; 94ACH(131)697] and books (83MI1, 83MI2; 84MI2; 85MI1; 87MI1, 87MI2; 88MI1; 90MI1) relating to intramolecular reversible and irreversible addition reactions have appeared.

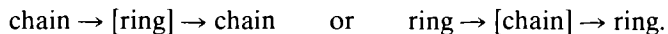
With regard to the survey of the literature data on this topic, the following aspects are given primary emphasis:

- (1) such structural features as the polarity of the $Q-X$ and $Y=Z$ bonds, the electronic and steric effects of the substituents at these bonds, the structures of the connecting fragment and the substituents in this fragment; other structural (internal) factors of the ring-chain equilibria and, when applicable, the rates of tautomeric interconversions;
- (2) the influence of external factors (temperature, the physical state of the substance, the properties of the solvents, the concentrations of solutions, and the presence of catalysts) on the ring-chain tautomeric equilibrium state and the rates of equilibration;
- (3) a search for conditions allowing selective preparation and/or selective isolation of the open-chain or cyclic isomers in the solid state;
- (4) estimation of the potential of spectroscopic and other methods for equilibrium and rate constant measurements.

The structural regularities governing ring-chain tautomeric equilibria are of great significance in the chemistry of heterocyclic compounds. In many cases, estimation of the ring-chain tautomeric equilibrium allows prediction of the ease of formation of a heterocycle and its stability (82UK1374). Intramolecular additions to polar multiple bonds are often followed by the elimination of water, hydrogen halide, or an alcohol molecule, thereby resulting in stable nonisomeric heterocycles (87T5171; 92KGS435).

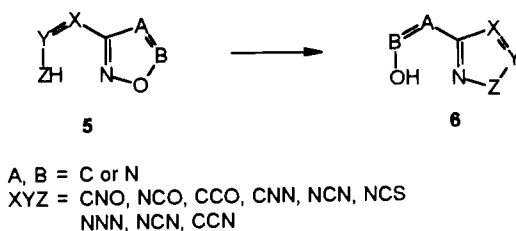
The structural factors controlling ring-closure reactions behave similarly in many significant chemical reactions or transformations, proceeding

through cyclic (or open-chain) transition states or intermediates. This is true for almost all chemical heterolytic transformations that occur via the following schemes:



Familiar examples of the former scheme include intramolecular catalysis with neighboring-group participation [76MI1; 80APO(17)183; 84MI3; 90MI1]; intramolecular migration of acyl and other groups (87MI2) through the formation of cyclic tetrahedral intermediates [85APO(21)37; 91CB1777]; hydroxy-, amino-, and mercaptoacyl-group incorporations into peptides and depsipeptides [93JCS(P1)819, and references cited therein]; and, similarly, the synthesis of macroheterocycles through ring-enlargement reactions via bicyclic tetrahedral intermediates (88T1573; 91MI1), which can be isolated in rare cases.

Most heterocyclic ring transformations, i.e., recyclization reactions (73MI1; 76AHC51; 82T3537; 84JHC627; 85UK1971; 94H2051), including S_N ANRORC recyclizations (78ACR462; 85T237), the second type of Boulton-Katritzky rearrangements (**5** \rightarrow **6**) [67JCS(C)2005; 76JCS(P1)315; 81AHC(29)141; 84JHC627; 90JCS(P2)1289, 90KGS1443; 93AHC(56)49, 93CB1835, 93H483, 93JCS(P2)1339] and similar azole-azine rearrangements [92JCS(P1)3069], proceed via the second scheme.



B. METHODS OF INVESTIGATION

The chemical and physical methods used to investigate the tautomerism of heterocycles, and their limitations, have been discussed in detail in an excellent monograph [76AHC(S)1].

The most powerful method currently available for the quantitative determination of ring-chain equilibrium constants is ^1H -NMR spectroscopy. Often, two pairs of indicator signals of both tautomeric forms have been used, thereby increasing the accuracy of equilibrium-constant determination. For structural analysis of the tautomers and quantitative measure-

ments, ^{19}F -NMR (84TL1019), ^{15}N -NMR [83HCA1537; 87DOK(296)1133; 90KGS1260; 91CB2065; 92KGS1689; 93T1257, 93T5327], ^{31}P -NMR (I-223), and ^{77}Se -NMR (81CL1353) methods have been employed. The great potential of ^{13}C -NMR spectroscopy has been demonstrated [87JCS(P2)969, 87T5171; 89JCS(P2)731] for investigation of the mechanisms of ring-closure reactions and structural elucidation of their transient intermediates. Some of these intermediates are produced by intramolecular NH-group addition to the C=O bond. By means of ^{13}C -NMR spectroscopy with cross-polarization and crystal-sample spinning under the magic angle (CP/MAS technique), the tautomeric structures and the ratios of the tautomers in solid-state mixtures have been determined (84CB702; 90ZOR2489; 92T4979). The free energies of activation (ΔG^\ddagger) for the acid-catalyzed ring-chain tautomeric interconversions of 1,3-diazolidines have been determined (87JOC68) by using ^1H -signal coalescence temperature measurements. Kinetic (k_1 , k_{-1}) and activation (ΔH^\ddagger , ΔS^\ddagger) parameters have been determined more accurately by means of standard line-shape analysis and/or saturation transfer applied to the ^1H (86LA1804) and ^{13}C signals [79JCS(P2)276; 85JA4320; 87LA547] in the NMR spectra of some oxocarboxylic acids [79JCS(P2)276], 5-hydroxypentanal (87LA547), or monosaccharides at different temperatures. These results are very sensitive to traces of impurities in the solvents used [79JCS(P2)276], and especially to proton microconcentrations. Less accurate determinations have been based on measurements of the linewidth at half-height (85JA2448). The complete study of a six-component equilibrium mixture of D-idose was performed with ^{13}C -enriched D-idose at position 1 by two-dimensional ^{13}C - ^1H shift correlation, very high-field (600 MHz) ^1H -NMR spectroscopy and by several double-resonance one-dimensional methods (86JOC2988). Two-dimensional long-range ^1H - ^{13}C -correlation spectra were used in the structure determination of *N*-(2-aminobenzoyl)-*N*-methylhydrazones and their cyclic isomers (90MI4) and for the investigation of other complex tautomeric systems [84CB702; 87JCS(P2)1477; 93M1053].

Investigation of ring-chain tautomeric equilibria in the gas phase under high vacuum by the use of mass spectrometry allows the separation of structural influences from solvation or intermolecular self-association effects (see, for example, 94H1093). The first investigation of ring-chain tautomerism by this method was reported in (71T4407). The number of papers published in this field has increased considerably during the past decade [83MI3, 83KGS1273; 84KGS1080; 86KGS1334; 88KGS746; 90T3683; 91JCS(P2)735, 91OMS(36)438; 93MI1, 93T1257]. The utilization of mass spectrometry to study ring-chain tautomerism in the gas phase is based on the observations of the proportions of the relative abundances of ions associated with one or another tautomeric form, especially when

low ionization energies (14 eV) are used (94H1093). The validity of this method largely depends on the reliability with which a daughter ion can be associated with a certain tautomeric species. The basic fragmentation pathway of, for example, perhydro-1,3-oxazines [91OMS(36)438] was studied in detail by using exact-mass measurement, metastable-ion analysis, and the collision-induced dissociation (CID) technique. The ring-chain tautomeric ratio varies considerably with the measurement conditions, i.e., with the source temperature and the energy of the ionizing electrons. When this ratio is measured as a function of the temperature of the ion source, approximate enthalpy differences (ΔH) can be estimated (90T3683). However, the use of mass spectroscopy does not permit determination of exact equilibrium constants [91OMS(36)438; 93MI1]. Unfortunately, no currently available method allows the performance of these measurements in the gas phase more accurately. For a more detailed discussion of the problem of the quantitative measurement of the tautomeric ratio in the gas phase through the use of mass spectrometry, see Bouchoux (88MI2, 88MI3) and Klyuev (89MI1). The ring-chain ratios of 2-aryl-substituted 1,3-oxazolidines measured in the gas phase by means of mass spectrometry (90T3683; 93MI1) resembled those determined in nonpolar solvents by means of ^1H -NMR and IR spectroscopy, and in certain cases they obeyed the equation $\log K_X = \log K_0 + \rho\sigma^+$ (where X is the substituent in the aryl group). In this way, electrophilic substituent constants for some heteroaryl groups were determined (94H1093) in the gas phase.

With regard to the results obtained by means of X-ray diffraction, the most interesting observation is the first example of ring-chain tautomers **7A** \rightleftharpoons **7B**, which exist as a remarkable **7A**:**7B** = 1:1 mixture in a single



crystal stabilized by a strong intermolecular hydrogen bond between the two tautomers (82CC25). In CDCl_3 , a temperature-independent equimolecular mixture of **7A** and **7B** was detected by ^{13}C -NMR, the interconversions of **7A** and **7B** being very slow. Addition of a trace amount of an acid catalyst accelerates the interconversions. However, recrystallization from a number of different solvents, with or without an acid catalyst, always led to the same solid containing an equimolecular mixture of **7A** and **7B**. This observation is good evidence that, despite the tautomer composition in the solution, the packing forces control the crystal structure and stoichiometry. Gener-

ally, the isolation of one isomer in the solid state does not necessarily imply its prevalence in the solution of the equilibrating tautomers (I-29; 90CB493, 90MI2).

Polarography has been used (86JOC3542) to determine very small concentrations of the open-chain tautomer of 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (see **46A** in Section II,B,1,b).

Gas-liquid chromatography (GLC) is rarely used for the study of ring-chain tautomer mixtures (84MI4).

Ring-chain equilibrium constants for **7A** \rightleftharpoons **7B** have been measured by $^1\text{H-NMR}$ as a function of pressure (1–2000 bar) to obtain the volumes of the intramolecular cyclization reaction and to compare them with those of the corresponding intermolecular analog [87JCS(P2)1477].

An algebraic description of ring-chain tautomerism is given in terms of graph theory, which was used for a classification of the tautomeric process (86MI2; 88MI5).

II. Intramolecular Reversible Addition Reactions to the C=O Group

A. OXOCARBOXYLIC ACIDS AND DERIVATIVES MODIFIED AT THE CARBOXYLIC GROUP

1. Oxocarboxylic Acids

Ring-chain tautomeric interconversions proceeding by intramolecular reversible addition reactions to the C=O group (Scheme 1) have been well studied, particularly with respect to the 3- and 4-oxocarboxylic acids containing five- or six-membered rings, respectively. Relatively few new investigations have appeared in the literature.

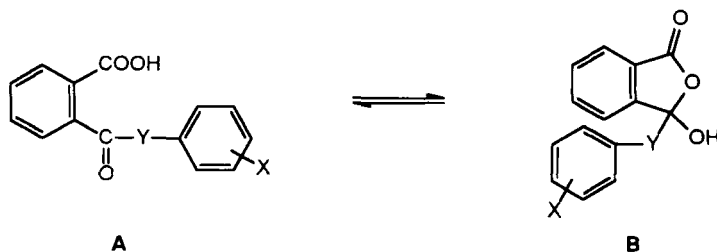
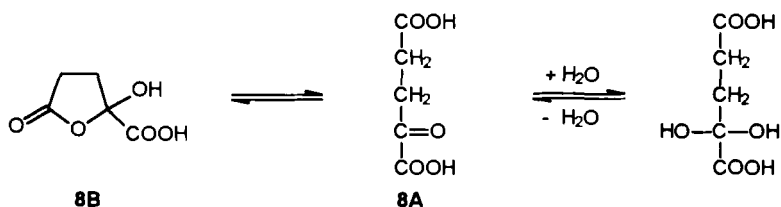
Ring-chain equilibria were observed (87ZOR902) in solutions of 1-carboxymethyl-1-formylcyclobutane. In a series of alkyl-substituted 4-oxobutanoic acids (91ZOB114), an increase in the number of alkyl substituents on the carbon atoms in the chain between the C=O and COOH



SCHEME 1

groups shifts the equilibrium toward the cyclic tautomer (Thorpe-Ingold effect). The ^{13}C -NMR data indicate that 3-trifluoroacetylpropionic and 2-trifluoroacetylbenzoic acids exist as stable cyclic isomers (88TL1029), due to the strong electron-withdrawing effect of the trifluoromethyl group.

The pH-dependent equilibrium $8\text{A} \rightleftharpoons 8\text{B}$, involving participation of the open-chain tautomer hydrate, was observed [75JBC(250)527] in aqueous solutions of 2-oxoglutaric acid.



9, Y = CH₂

10, Y = CO

Ring-chain equilibrium constants² K_T have been determined by using IR and ^1H -NMR spectroscopy [93JCS(P2)635] for a series of 2-phenylacetylbenzoic (**9**) and benzyl-2-carboxylic (**10**) acids substituted in the phenyl group. A good linear correlation between K_T and the constants σ or σ'' for the substituents X was obtained. As shown in Table I, for acids **9** the correlations are generally better with σ'' than with σ , whereas the converse is true for acids **10**. The equilibrium constant $K_T = 5.7$ for **9** (X = H) in chloroform solution is considerably greater than $K_T = 1.4$ for **10** (X = H) under the same conditions. Bowden and Malik explained [93JCS(P2)635] that the change from PhCH₂ to PhCO on going from acid **9** to **10** results in a more electron-withdrawing and bulkier substituent at

² Throughout this paper, $K_T = [\text{B}]/[\text{A}]$, unless another meaning is given.

TABLE I
CORRELATION PARAMETERS OF RING-CHAIN EQUILIBRIUM CONSTANTS OF 2-
PHENYLACETYL BENZOIC (**9**) AND BENZYL-2-CARBOXYLIC (**10**) ACIDS^a

Equilibrium	Solvent	(<i>t</i> °C)	σ or σ''	$\log (K_T)_0$	ρ	r	s
9A \rightleftharpoons 9B	MeOH	25	σ	0.485	0.490	0.971	0.049
			σ''	0.465	0.567	0.966	0.062
	CHCl ₃	35	σ	0.78	0.400	0.956	0.050
			σ''	0.765	0.478	0.989	0.029
10A \rightleftharpoons 10B	CHCl ₃	35	σ	0.14	0.495	0.991	0.027
			σ''	0.12	0.557	0.961	0.066

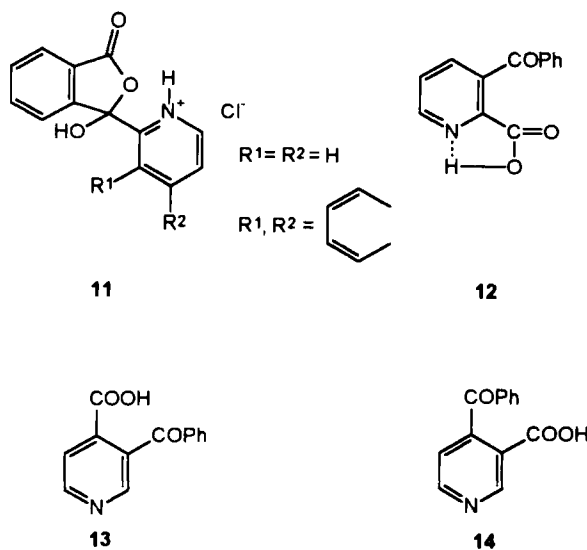
^a Data from Bowden and Malik [93JCS(P2)635]. The equilibrium constants were determined in CHCl₃ by IR spectroscopy, and in MeOH by ¹H-NMR. $n = 8$ (X = H, 3-Me, 4-Me, 3-MeO, 4-MeO, 3-Cl, 4-Cl, 4-Br). Henceforth r is the correlation coefficient, s is the standard error, and n is the number of derivatives studied.

the intramolecularly reacting C=O group, and they reasoned these two factors affect the stability of the cyclic tautomer in opposite directions. We cannot agree with the latter statement because both factors should favor the cyclic tautomer [I-246, 251; 71JCS(B)1390, 71JCS(B)1395]. Actually, there is little difference in the steric demands of the benzyl and benzoyl groups; but the observed decrease in cyclic tautomer stability on going from **9** to **10** could be explained by the free-energy gain in favor of the open-chain form **10A**, which is caused by the conjugation in the PhCOCOAr bond system in **10A**.

2-(2-Pyridylcarbonyl)- and 2-(2-quinolylcarbonyl)benzoic acids possess the open-chain structure in the solid state (84KGS1231). In dioxane solution, the ring-chain equilibrium is observed. Protonation of the pyridine or quinoline ring nitrogen atom leads to the formation of the protonated cyclic forms **11**. Evidently, protonation stabilizes the tautomer that is the stronger base, i.e., the cyclic form.

In the solid state, 3-benzoylpyridine-2-carboxylic acid exists as the open-chain form **12**, stabilized by an intramolecular hydrogen bond. In dioxane solution, the ring-chain equilibrium was observed. The IR spectrum reveals that the hydrochloride of acid **12** exists as a mixture of the protonated cyclic and open-chain forms (86MI1).

3-Benzoylpyridine-4-carboxylic (**13**) and 4-benzoylpyridine-3-carboxylic (**14**) acids possess the open-chain structure both in the solid state and in dioxane solution. Their hydrochlorides retain the open-chain structure. The IR spectrum of the hydrochloride of acid **14** displays a weak C=O band at 1805 cm⁻¹, indicating the presence of a small admixture of the protonated cyclic form (86KGS80).



8-(2-Pyridylcarbonyl)- and 8-(2-quinolylylcarbonyl)naphthoic acids have been isolated as cyclic isomers in the solid state and are also present in dioxane solutions; the equilibria are shifted fully in favor of the cyclic forms (84KGS1231).

2. Chlorides and Azides

Unlike the oxocarboxylic acids, which form the cyclic tautomer as a result of intramolecular nucleophilic addition of a COOH group to the C=O bond, the ring closure of 4- or 5-oxoacyl chlorides takes place by intramolecular electrophilic addition of a COCl group to the keto or aldehyde C=O bond (Scheme 2). Structural factors increasing the electrophilicity of the COCl group and/or the nucleophilicity of the oxygen atom in the C=O group favor ring formation. The stability of the cyclic chlorides of oxocarboxylic acids is mainly attributable to the high electrophilicity of the COCl

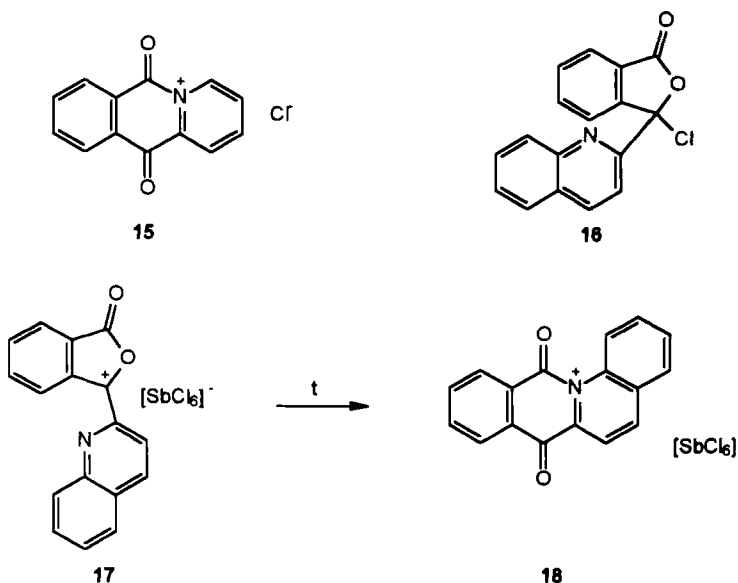


SCHEME 2

group, which is afforded by the $-I$ effect of the chlorine atom when the structure of the chain connecting these interacting groups and that of the substituent at the keto group allow a ring closure. With the exception of a few special cases, 4-oxocarboxylic acid chlorides have been obtained only as cyclic isomers and the tautomeric equilibrium has not been detected (I-41). The data on the structures of a large number of 4- or 5-oxoacyl chlorides and the chlorides of some dicarboxylic acid half-esters are compiled in a review [80IJC(B)473], but in some cases the assignment of the open-chain or cyclic structure to the compounds discussed in this review is based only on their chemical properties.

2-Trichloroacetylbenzoic acid reacts with thionyl chloride to produce a mixture of both chloride isomers. However, the open-chain isomer readily transforms into the cyclic form, which was the only isomer isolated from the mixture in the solid state. The presence of the open-chain isomer in the reaction product mixture, which is generally uncharacteristic for 2-acylbenzoyl chlorides, may be caused by the strong $-I$ effect of the trichloromethyl group which decreases the nucleophilicity of the ketone oxygen atom (88MI4).

The reaction of 2-(2-pyridylcarbonyl)benzoic acid with thionyl chloride afforded 6,11-dioxobenzo[*c*]quinolizinium chloride (**15**) (82ZOR2226) instead of the expected chlorolactone. However, when the 2-pyridyl substituent was replaced by a 2-quinolyl group, this reaction proceeded as



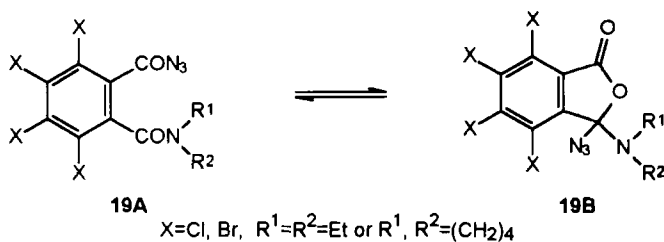
usual for 2-acylbenzoic acids and led to chlorolactone **16** (94KGS499). The hexachloroantimonate obtained from this lactone and SbCl_5 underwent the thermal isomerization **17** \rightarrow **18** in the solid state.

The chlorides of 3-benzoylpyridine-2-carboxylic (86MI1), 4-benzoylpyridine-3-carboxylic, 3-benzoylpyridine-4-carboxylic (86KGS80), and 5-arylpyridazine-4-carboxylic (85LA167) acids were isolated only as cyclic chlorolactones. The fluorides of levulinic, 3-benzoylpropionic, and 2-acetyl- and 2-benzoylbenzoic acids were also obtained (84TL1019) only in cyclic form.

4-Aroylbutyric acids react with oxalyl chloride to produce mixtures of open-chain isomers of the chlorides and unsaturated lactones, the latter being formed by dehydrochlorination of the cyclic isomers of the chlorides [86JCS(P2)355]. It was presumed in that paper that the two chloride isomers were formed from the initial acids in two independent competitive reaction pathways.

The chlorides of 2-(2-pyridylcarbonyl)- and 2-(2-quinolylcarbonyl)biphenyl-2'-carboxylic acids were obtained (84MI5) only as open-chain isomers. Examples of seven-membered chlorolactone formation in the series of 6-oxocarboxylic acid chlorides are not known.

Ring-chain tautomerism caused by the migration of an azido group has been observed rather rarely. By means of IR spectroscopy, the equilibrium **19A** \rightleftharpoons **19B** was detected [81JCS(P1)2884] in benzene solutions of *N,N*-disubstituted tetrahalogenophthalamic acid azides. Mixtures of open-chain and cyclic isomers of 2-benzoylbenzoyl azide were obtained [88JCS(P1)2149], from which only isolation of the cyclic isomer succeeded.



3. Amides

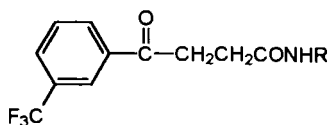
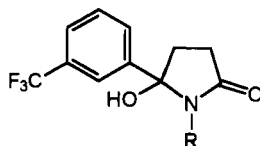
In contrast with the oxocarboxylic acids, which readily participate in tautomeric equilibria in solution, their open-chain and cyclic *N*-unsubstituted and *N*-monosubstituted amide isomers are more stable. In most cases, the tautomeric equilibrium (Scheme 3) is not observed in neutral aprotic solvents at ambient temperature. In protic solvents, e.g., CD_3OD , intercon-



SCHEME 3

version of the tautomers takes place at a measurable rate (usually slow on the ^1H -NMR time scale). A considerable acceleration may be achieved by adding a basic catalyst to the solution. In aprotic solvents, slow ring-chain equilibration may be observed for the oxocarboxamides, whose molecules contain an additional amino group sufficiently basic to act as the basic catalyst, e.g., *N*-monosubstituted 3-benzoylpyridine-2-carboxamides in dioxane solution (86MI1, 86ZOR225).

N-Unsubstituted and *N*-mono-*n*-alkyl-substituted 3-(3-trifluoromethylbenzoyl)propionamides were obtained in the cyclic form **20B** ($\text{R} = \text{H}, \text{Me}, \text{Et}, \text{Pr}, \text{Bu}$). Amides containing branched alkyl substituents on the nitrogen atom and *N,N*-dimethylhydrazide exist (85JMC28) as the open-chain isomers **20A** ($\text{R} = i\text{-Pr}, \text{sec-Bu}, i\text{-Bu}, \text{cyclo-C}_6\text{H}_{11}, \text{NMe}_2$). For the open-chain isomers **20A**, a typical acyl $\text{C}=\text{O}$ signal at 190 ± 5 ppm was observed in the ^{13}C -NMR spectrum, while the cyclic isomers gave the carbinolamine $[\text{C}(\text{OH})\text{NR}]$ ^{13}C signal at 90 ± 2 ppm.

**20A****20B**

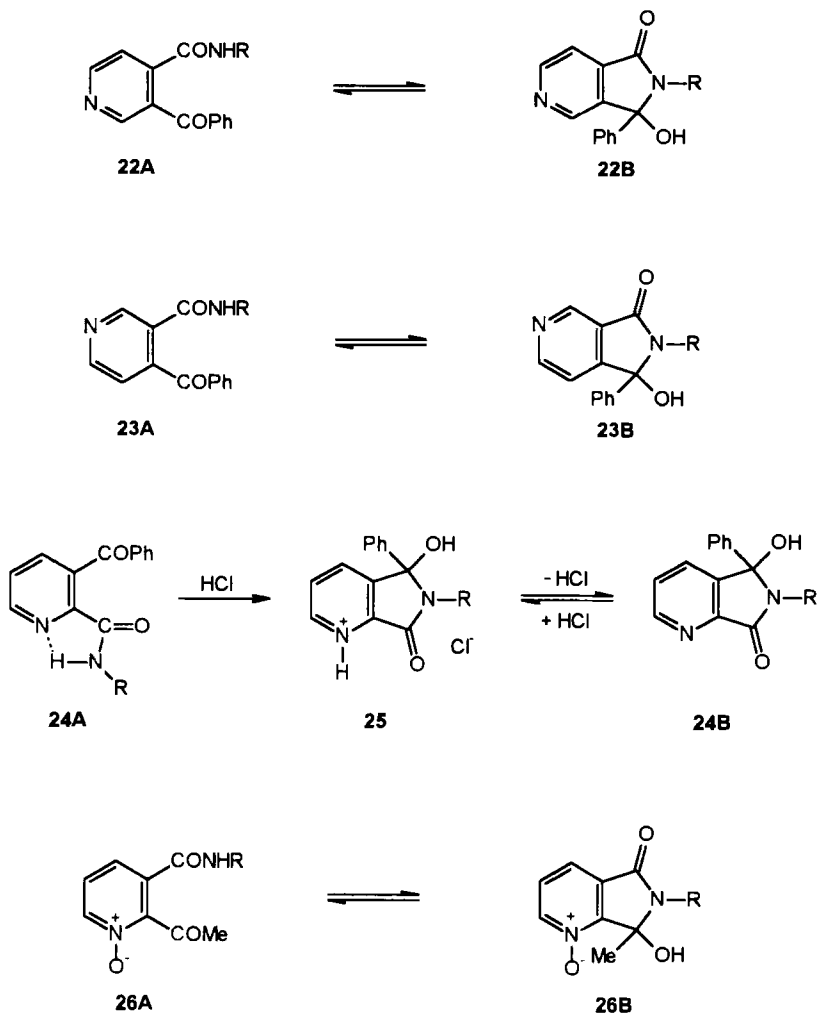
The stable open-chain isomers of 2-acylbenzamides **21A** (Table II) can generally be obtained only by the introduction of sterically demanding substituents either on the nitrogen atom (*t*-alkyl) or on the keto group (2,6-dimethylphenyl) (I-75). The signals of the *t*-butyl protons in the ^1H -NMR spectra differ (slow equilibration on the ^1H -NMR time scale) for the ring and open-chain tautomers of *N*-*t*-butyl-2-benzoylbenzamides and pyridine-carboxamides in CD_3OD solution (87MI3). As may be seen in Table II, the introduction of a chlorine atom at position 3 of the phthaloyl ring shifts the equilibrium strongly in favor of the cyclic tautomer **21B**; this may be caused by the $-I$ effect of the chlorine atom on the $\text{C}=\text{O}$ group in the open-chain isomer molecule, and by the steric assistance [sometimes called the "support" effect (I-259)] of the chlorine atom which creates steric strain

TABLE II
RING-CHAIN EQUILIBRIUM CONSTANTS^a OF SUBSTITUTED *N*-*t*-BUTYL 2-BENZOYL BENZAMIDES AND BENZOYL PYRIDINE CARBOXAMIDES

X	K_T
H	0.56
3-Cl	1.54
4-Cl	0.75
3-NO ₂	0.08
4-NO ₂	1.00
5-NO ₂	1.34
6-NO ₂	0.09
4-aza	0.07
5-aza	0.25
6-aza	0.06 ^b

^a Data from Valters *et al.* (87MI3). Determined by ¹H-NMR in CD₃OD at 30°C 5 hours after dissolution. ^b The open-chain tautomer of *N*-*t*-butyl-3-benzoylpyridine-2-carboxamide is stabilized by an intramolecular hydrogen bond (86MI1).

in the open-chain molecule and thereby favors intramolecular cyclization. The shift of the chlorine atom from position 3 to position 4 effectively cancels out its stabilizing influence in favor of the cyclic form. It is rather difficult to explain the influence of the nitro group as a substituent in the phthaloyl ring because both interacting centers (CONHR and C=O) are affected. A nitro group at position 5 is the most favorable for the cyclic tautomer because its $-M$ effect increases the C=O group carbon atom electrophilicity in the open-chain tautomer. In the series of *N*-*t*-butylbenzoylpyridine carboxamides, the ring-chain equilibrium is shifted toward the open-chain tautomer, the cyclic tautomer being mostly stabilized for the 5-aza isomer. Evidently, this may be caused by the fact that the 4-pyridyl group possesses a greater $-M$ effect than the 3-pyridyl group (91ACS273) with respect to influence on the C=O group electrophilicity in the open-chain tautomer molecule. The stabilization of the 6-aza isomer



open-chain tautomer is caused by an intramolecular hydrogen bond (86MI1).

N-Benzylamides **22** and **23** ($\text{R} = \text{PhCH}_2$) are isolated as stable cyclic isomers **22B** and **23B**, whereas *N*-*t*-butylamides possess open-chain structures **22A** and **23A** ($\text{R} = t\text{-Bu}$) in the solid state (86KGS80). The hydrochloride of the amide **22A** ($\text{R} = t\text{-Bu}$) retains the open-chain structure in the

solid state, but the salt of **23A** ($R = t\text{-Bu}$) was isolated in cyclic form. ^1H -NMR spectroscopy was used to investigate the influence of *N*-protonation on the ring-chain equilibria of both amides **22A** and **23A** ($R = t\text{-Bu}$) (87MI3) in trifluoroacetic acid solutions in CD_3OD . In both cases, the more acidic the solution is, the more strongly the equilibrium is shifted toward the protonated cyclic tautomer, this regularity being more pronounced for amide **23A**. However, on continued increase of the CF_3COOH concentration, the equilibrium constant passed through a maximum and began to decrease, which appears to be caused by the second protonation of the cyclic tautomer (see 77KGS763; 79KGS780).

Depending on the *N*-substituent structure, 3-benzoylpyridine-2-carboxamides possess a cyclic (**24B**; $R = \text{H}, \text{PhCH}_2$) or an open-chain (**24A**; $R = i\text{-Pr}, t\text{-Bu}, \text{Ph}, 4\text{-MeOC}_6\text{H}_4$) structure in the solid state, the latter being stabilized by an intramolecular hydrogen bond (86MI1, 86ZOR225). Following protonation, the ring closure **24A** \rightarrow **25** takes place. Careful deprotonation of the salts **25** under mild conditions allows isolation of the free bases with cyclic structure **24B** ($R = i\text{-Pr}, \text{Ph}, 4\text{-MeOC}_6\text{H}_4$), or of the mixture **24A** + **24B** when $R = t\text{-Bu}$. The cyclic isomers **24B** ($R = i\text{-Pr}, \text{Ph}, 4\text{-MeOC}_6\text{H}_4$) are unstable and readily transform into the open-chain isomers on recrystallization or heating. They have broad melting points, due to thermal isomerization before or during melting. The slowly attained (in 5 days) equilibrium **24A** \rightleftharpoons **24B** in solution in dioxane was observed to shift toward the open-chain tautomer.

2-Acetylpyridine-3-carboxamide *N*-oxides were isolated as cyclic isomers **26B** ($R = i\text{-Pr}, t\text{-Bu}$) in the solid state (87MI4). In CD_3OD solution, the isopropyl derivative retains the cyclic structure, but for the *t*-butyl derivative a ring-chain equilibrium was observed ($K_T = 1.10$; ^1H -NMR).

Both isomers of 5-benzoylpyridazine-4-carboxamide were isolated in the solid state (85LA167). The open-chain isomer obtained in the homolytic benzoylation of pyridazine-4-carboxamide is unstable and readily undergoes ring closure during recrystallization or chromatographic purification.

4-Benzoyl-2,2,4,4-tetramethylbutyramide was obtained (84BAP335) only as the cyclic isomer, whereas both isomers were isolated for 4-benzoyl-3,3-dimethylbutyramide. The ring-chain equilibrium ($K_T \sim 1$) was rapidly attained in a solution of ether in the presence of traces of an acid catalyst, but this equilibration was accompanied by dehydration of the cyclic tautomer. The same equilibrium was reached, but more slowly, in the presence of basic catalysts, such as tertiary amines.

2-(2-Pyridylcarbonyl)- and 2-(2-quinolylcarbonyl)biphenyl-2'-carboxamides exist (84MI5) only as open-chain isomers. Ring closure takes place neither in the presence of basic catalysts nor on protonation of the pyridyl or quinolyl ring nitrogen atom.

B. HYDROXY ALDEHYDES AND KETONES AND RELATED COMPOUNDS

1. Derivatives Containing a C—OH Group

Ring-chain tautomerism in which a ring closure occurs via intramolecular addition of an OH group to a C=O bond (Scheme 4) is observed widely in organic chemistry. This type of tautomerism is sometimes called ketolactolic, keto-lactolic, or oxo-cyclo tautomerism. The ring tautomers are usually referred to as cyclic hemiacetals or hemiketals.

The mutarotation of aldoses and ketoses is a very important example of these tautomeric interconversions. Because a series of reviews (I-98; 84MI6) has been dedicated to this problem in sugar chemistry, we will not discuss it here. Recently, significant progress has been made in the study of the kinetics of the tautomeric interconversions of monosaccharides by using dynamic ^1H and ^{13}C -NMR spectroscopy and GLC methods (82JA4037; 85JA2448, 85JA4320; 86JOC2694).

a. *Addition of C_{sp^3} —OH.* By means of line-shape analysis of ^{13}C -NMR spectra recorded in acidified D_2O solution at different temperatures, the rate constants for the tautomeric ring-chain interconversions of 5-hydroxypentanal have been determined (87LA547). Simultaneous hydration of the open-chain tautomer proceeds at a lower rate. At 43.7°C , $K_{\text{T}} = 24.2$ (in D_2O). The increase of temperature shifts the equilibrium toward the open-chain tautomer (at 62.1°C , $K_{\text{T}} = 10.6$).

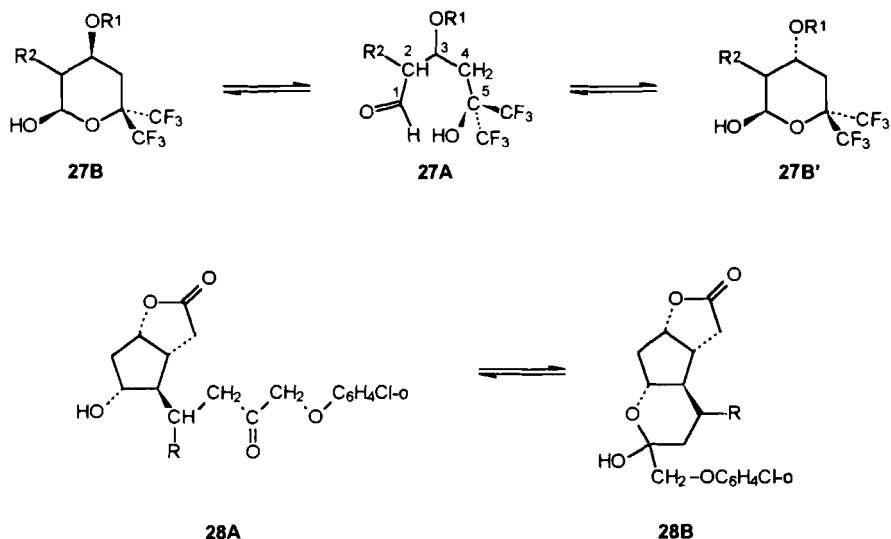
The products obtained in tetrahydropyran-2-one reactions with RLi were mixtures of the corresponding hydroxyketones and their cyclic tautomers (90JA2746). In CDCl_3 solution, when $\text{R} = \text{Me}$, $K_{\text{T}} = 0.22$; when $\text{R} = \text{Bu}$, $K_{\text{T}} = 0.2$; and when $\text{R} = \text{Ph}$, $K_{\text{T}} = 0.1$.

The influence of solvent polarity on the ring-chain equilibrium is contradictory for hydroxy aldehydes or ketones of different structures (I-101).

^1H -NMR spectroscopy of CDCl_3 solution showed that a mixture of the epimers **27B** and **27B'** (3:2) was obtained [90JCS(P1)617] in the presence of $\sim 20\%$ of open-chain tautomer **27A** ($\text{R} = t\text{-BuMe}_2\text{Si}$; $\text{R}^1 = \text{H}$). In tetrahydrofuran- D_8 , the epimer ratio was 1:1 and the open-chain tautomer could not be detected at all. Replacement of one of the trifluoromethyl groups



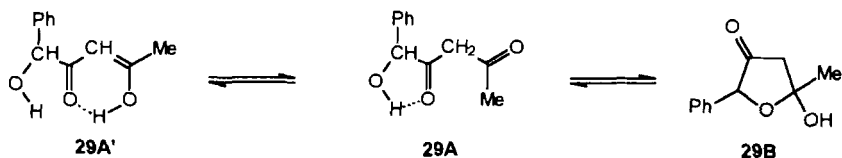
SCHEME 4



by a phenyl group stabilizes the open-chain tautomer, but the ring-chain equilibrium depends on the mutual configuration of the two diastereomeric centers (C-3 and C-5). Higher solvent polarity favors the cyclic tautomer.

Introduction of a methoxy group (**28**, R = OMe) into the aryloxy side chain in the series of prostaglandin intermediates **28** has been found [90JCS(P1)751] to affect the ring-chain equilibrium significantly in favor of the cyclic tautomer. In CDCl₃, when R = H, $K_T = 1$, and when R = OMe, $K_T = 9$.

Simultaneous ring-chain and keto-enol tautomeric equilibria were observed (90ZOR2489) in solutions of 5-hydroxy-5-phenylpentane-2,4-dione **29**. Increase of the solvent polarity and proton-accepting ability in the series

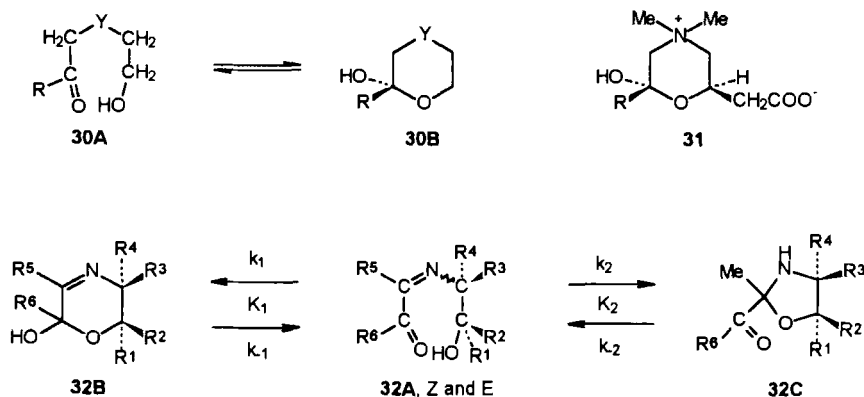


CCl₄ < CDCl₃ < (CD₃)₂CO < (CD₃)₂SO stabilizes the diketo tautomer **29A** and mostly the cyclic tautomer **29B**; this is caused by the ability of proton-accepting solvents to destroy the intramolecular hydrogen bond stabilizing the chelate **29A'**.

It has been shown (82CC25) by means of ¹³C-NMR spectroscopy that 2-*exo*-bromo-7,7-dichloro-3-*endo*-hydroxybicyclo[3.2.0]heptan-6-one (**7B**; see Section I,B) exists in CDCl₃ solution as an equimolecular mixture of

tautomers **7A** and **7B** that is stabilized by a strong intermolecular hydrogen bond, thereby giving rise to dimeric species **7A**...**7B**. When a trace of toluene-*p*-sulfonic acid was added to the CDCl_3 solution, the equilibrium constant was found to differ from unity and to be temperature-dependent. Increasing the concentration of the acid catalyst or the temperature led, as expected, to the coalescence of the tautomer signals, the equilibration becoming fast on the NMR time scale. It follows from the data (82CC25) that an increase in temperature stabilizes the cyclic tautomer **7B**, which seems surprising for such a tautomeric system. The solvent used in [87JCS(P2)1477] was 20% w/w $(\text{CD}_3)_2\text{SO}-\text{CDCl}_3$, which differs from that (CDCl_3 plus trace amounts of toluene-*p*-sulfonic acid) in (82CC25), but this difference cannot be the cause of the opposite direction of the equilibrium temperature dependence. The second investigation showed the usual temperature dependence: at -8°C , $K_T = 3.57$, and at 32°C , $K_T = 1.85$ [in 20% w/w $(\text{CD}_3)_2\text{SO}-\text{CDCl}_3$].

The equilibrium $\mathbf{30A} \rightleftharpoons \mathbf{30B}$ ($\text{Y} = \text{O}$, $\text{R} = \text{Me}$) was detected (87



UKZ746) for 2-hydroxy-2-methyl-1,4-dioxane. The ring-chain equilibrium constants for the *N*-aroylmethyl-*N*-(2-hydroxyethyl)-*N,N*-dimethylammonium (aroylcholinium) salts $\mathbf{30A} \rightleftharpoons \mathbf{30B}$ ($\text{Y} = \text{NMe}_2$, $\text{R} = \text{XC}_6\text{H}_4$) were determined (91ACS558) to be in the range from 1.4 to 176 on going from electron-donating to electron-withdrawing substituents X. For the structurally similar hemiacylcarnitiniums **31** ($\text{R} = \text{Me}$, Et, Ph), only the cyclic isomer was detected in the solid state or in solution by means of IR and ^1H -NMR spectroscopy (92JOC3426). For these compounds, the ring-chain equilibrium constant has been estimated to be ~ 1000 .

An extension (90TL4211; 92JOC2446) of the initial investigations (86TL1381, 86TL4217) of the product structures in the reactions of 2-aminoethanol and its *C*-substituted derivatives with 1,2-diketones shows the interesting phenomenon of a three-component ring-chain-ring tauto-

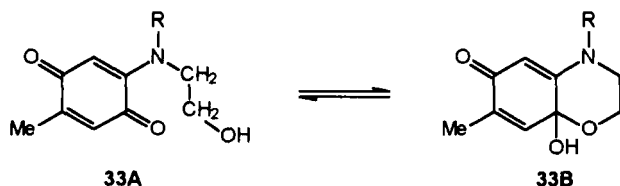
TABLE III
RATE AND EQUILIBRIUM CONSTANTS^a AND FREE ENERGY DIFFERENCES FOR THE EQUILIBRIUM
32B \rightleftharpoons **32A** \rightleftharpoons **32C** (R¹ = H; R⁵ = Me)

R ²	R ³	R ⁴	R ⁶	$k \times 10^3 \text{min}^{-1}$				K_1 (k_1/k_{-1})	K_2 (k_2/k_{-2})	kcal/mol		
				k_1	k_{-1}	k_2	k_{-2}			ΔG_1^0	ΔG_2^0	$\Delta G_2^0 - \Delta G_1^0$
H	H	H	Me	1.4	1.0	69.0	42.0	1.40	1.64	0.21	0.31	0.10
Me	H	H	Me	1.2	1.8	0.9	0.4	0.67	2.25	0.24	0.48	0.72
H	H	Me	Me	10.0	51.0	31.0	4.7	5.00	6.59	0.98	1.15	0.17
H	H	H	Ph	40.0	110	15.0	6.2	0.36	2.42	0.62	0.55	1.17
Me	H	H	Ph	7.6	15.0	7.8	4.2	0.51	1.86	0.43	0.38	0.79
H	Me	H	Ph	40.0	30.0	94.0	11.0	1.33	8.54	0.17	1.31	1.15

^a Data from Alcaide *et al.* (92JOC2446). Determined by ¹H-NMR in CDCl₃ at 35°C.

merism. The equilibrium observed is a result of competing intramolecular OH-group additions to the C=O or C=N bond following 6-*exo-trig* or 5-*endo-trig* cyclization pathways in accordance with the Baldwin rules (76CC234; 92MI1; 93ACR476). The evolution of the ^1H - and ^{13}C -NMR spectra in solution clearly indicated the equilibrium $\mathbf{32B} \rightleftharpoons \mathbf{32A} \rightleftharpoons \mathbf{32C}$. This three-component equilibrium was observed only when $\text{R}^5 = \text{Me}$. When $\text{R}^5 = \text{R}^6 = \text{Ph}$, the two-component equilibrium $\mathbf{32A} \rightleftharpoons \mathbf{32B}$ was rapidly attained. Dimethyl substitution on the carbinolic carbon ($\text{R}^1 = \text{R}^2 = \text{Me}$) permits formation of the oxazolidine tautomer $\mathbf{32C}$ only, whereas dimethyl substitution on the imine carbon ($\text{R}^3 = \text{R}^4 = \text{Me}$) led not to the corresponding oxazolidine $\mathbf{32C}$, but to the oxazine $\mathbf{32B}$. Table III demonstrates that formation of the oxazolidine ring $\mathbf{32C}$ is favored over the open-chain tautomer $\mathbf{32A}$ and the oxazine ring $\mathbf{32B}$. This is corroborated by the $(\Delta G_2^\circ - \Delta G_1^\circ)$ values, which reveal a shift of the equilibrium toward the five-membered ring by 0.1–1.15 kcal/mol. One methyl substituent α to the nitrogen atom (R^3 or $\text{R}^4 = \text{Me}$) strongly stabilizes cyclic tautomers $\mathbf{32B}$ or $\mathbf{32C}$, whereas methyl substitution on the carbon α to the oxygen atom ($\text{R}^2 = \text{Me}$) seems to slow down the ring-opening and ring-closing processes, exerting no significant effect on the stability of the cyclic tautomers. It is unclear whether the tautomeric equilibrium is shifted toward the five-membered ring tautomer because the 5-*endo-trig* process is thermodynamically favored over the 6-*exo-trig* process or because the favored *E*-isomer of $\mathbf{32A}$ cannot lead to the six-membered ring. The latter assumption appears more likely. In its favor, an inverse correlation has been observed between $\Delta G_{Z/E}$ for the open-chain isomers $\mathbf{32A}$ and the rate of 5-*endo-trig* closure (k_2). The derivative $\mathbf{32}$ ($\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{H}$; $\text{R}^2 = \text{R}^5 = \text{Me}$; $\text{R}^6 = \text{Ph}$), having the more favored *Z*-isomer of $\mathbf{32A}$, exhibits a faster ring closure ($k_2 = 94 \times 10^{-3} \text{ min}^{-1}$). The stereoselectivity of oxazine-ring $\mathbf{32B}$ formation has been considered (92JOC2446) as a function of the substituent pattern, the stereoelectronic effects (83MI1) being taken into account as well.

The ^1H -NMR spectra were recorded at different temperatures to determine the ring-chain equilibrium constants in solutions of 2-*N*-(2-hydroxyethyl)amino-5-methyl-1,4-benzoquinones $\mathbf{33}$ (93M1053). Greater



steric demands of the substituent R on the nitrogen atom shift the equilibrium in favor of the cyclic tautomer $\mathbf{33B}$. In $(\text{CD}_3)_2\text{SO}$ solution at 26°C ,

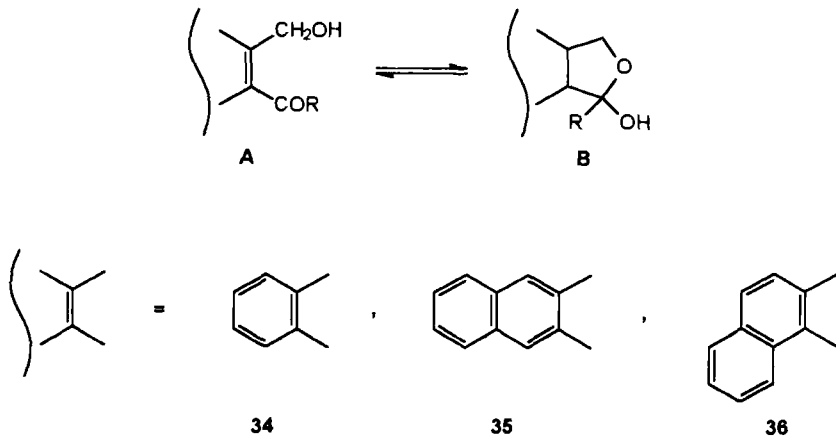


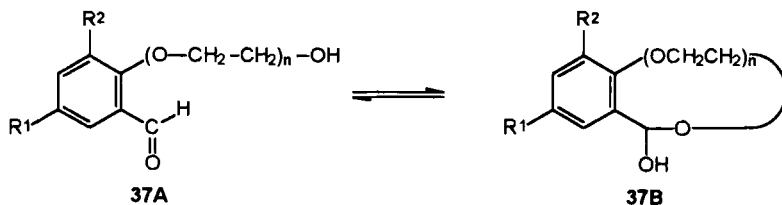
TABLE V
RING-CHAIN EQUILIBRIUM CONSTANTS^a FOR 2-
(2-HYDROXYETHOXY)BENZALDEHYDES (**37A** \rightleftharpoons **37B**) IN
VARIOUS SOLVENTS

R ¹	R ²	K _T		
		in (CD ₃) ₂ SO	in CD ₃ CN	in CDCl ₃
H	NO ₂	11.4	2.9	1.6
H	Br	1.0	1.0	1.0
H	Ph	0.4	0.24	0.1
H	Me	0.6	—	1.0
Br	Br	7.1	2.3	0.9
Cl	Cl	6.8	2.1	0.7
I	I	7.4	2.6	1.2

^a Data from Jones and Jaglowsky (90JOC3891); determined by ¹H-NMR.

tives is accompanied by a shift in the equilibrium toward the open-chain tautomer. It is supposed (84T1667) that a five-membered ring [*b*]fused to the naphthalene system involves a greater angular strain than that is the case with fusion to the benzene system because the naphthalene derivatives deviate from the ideal hexagonal shape of the benzene ring. For the [*a*]fused derivatives **36**, the opposite effect was observed, obviously because of the steric-assistance effect (I-259) of the naphthalene *peri*-proton (8-*H*) stabilizing the cyclic tautomer **36B**. With regard to the substituents R on the C=O group (Table IV), the open-chain tautomer is more stabilized by the phenyl group, due the conjugation in the open-chain molecule, and by the 1-naphthylmethyl or *o*-tolylmethyl groups, due to steric hindrance.

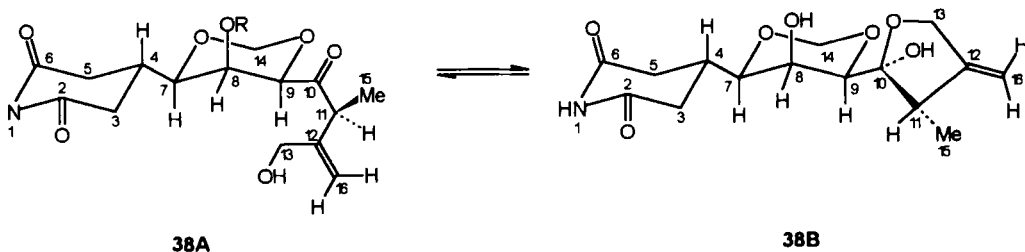
Another case of an *ortho*-substituent steric-assistance effect has been described (90JOC3891) for the rather rare situation of a ring-chain equilibrium involving a seven-membered ring closure. The equilibrium was ob-



served (Table V) in solutions of 2-(2-hydroxyethoxy)benzaldehydes **37** ($n = 1$) having substituents R² at position 3. The unsubstituted (R¹ = R² = H) or only 5-substituted (R² = H) compounds exist exclusively in the

open-chain form. Equilibrium involving formation of the ten-membered ring **37B** ($n = 2$) was not observed. A good correlation was noted between the percentage of the cyclic tautomer **37B** ($n = 1$) and the steric size of the substituent R^2 , expressed by using the Charton parameter ν (75JA1552). As may be seen in Table V, an increase in solvent polarity and proton-accepting ability in most cases stabilizes the cyclic tautomer **37B** ($n = 1$) (containing the more acidic OH group) over the open-chain tautomer [for pK_a data on similar open-chain and cyclic tautomers, see Harron *et al.* (81JOC903)]. A rationalization of the solvent effect on the basis of intermolecular hydrogen-bond formation fits all but the 3-bromo and 3-methyl derivatives. An equilibrium involving seven-membered ring formation was found [83BSF(2)269] in solutions of the structurally similar 6-hydroxy-4-oxahexanal and -heptanal.

Sesbanimide is a novel cytotoxic compound isolated from *Sesbania punicea* seeds [84JCS(P1)1311]. According to high-field ^1H - and ^{13}C -NMR spectroscopy, in solution a solvent-dependent equilibrium exists between the



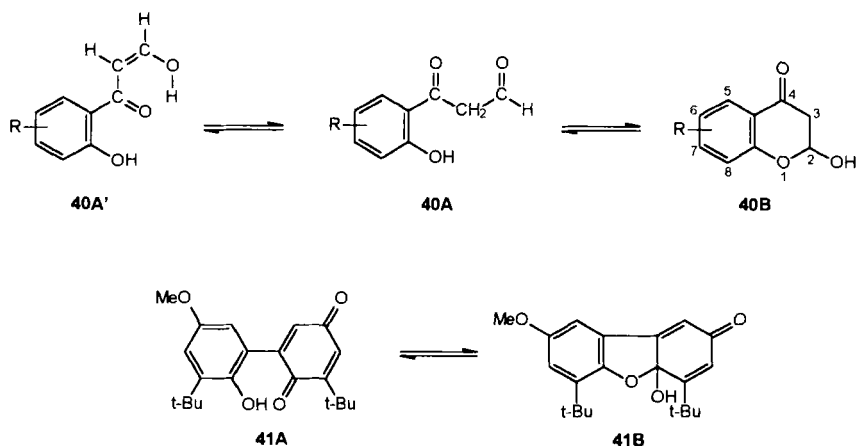
γ -hydroxyketone (**38A**) and ring-closed hemiacetal (**38B**). In CDCl_3 , the hemiacetal form exists alone. More polar solvents lead to the following equilibrium constants: in pyridine, $K_T = 3$; in methanol, $K_T = 2$; and in dimethyl sulfoxide (DMSO), $K_T = 1$.

b. *Addition of Phenolic OH.* Examples of an intramolecular addition of a phenolic OH group to an aldehyde or ketone $\text{C}=\text{O}$ bond to form five- or six-membered rings are numerous (I-104).



2*H*-Chromene derivatives **39B** ($R^1 = H$) were obtained (88KGS460) in the cyclization of some substituted *o*-hydroxycinnamic aldehydes **39A** ($R^1 = H$); this cyclization proceeds spontaneously during isolation in dimethylformamide (DMF) and DMSO solutions or on heating. The presence of an alkyl substituent in the side chain ($R^2 = Me, Et$) and/or of a sterically bulky substituent at position 3 of the benzene ring ($X = Br, MeO, NO_2$) favors the ring closure. Some of these cyclic isomers exhibit double melting points, caused by thermal isomerization with ring opening. The ring-chain equilibrium **39A** \rightleftharpoons **39B** ($X = Y = H$; $R^1 = 4-ZC_6H_4$, $Z = H, Me, MeO, O^-$; $R^2 = H, Me$) was observed (80JA5838; 82JOC3730; 85JA5459, 85JOC5656) during investigation of the kinetics of covalent hydration of the flavylum ion in aqueous solution. Up to seven intermediates were detected in these reactions, depending on the pH of the solution. Introduction of an electron-donating substituent Z ($R^1 = 4-ZC_6H_4$) stabilizes the open-chain form **39A**. Increase of the pH of the solution ($pH > 8$) shifts the equilibrium toward the open-chain form owing to the ionization of the more acidic phenolic OH group. Such a shift of the equilibrium is generally characteristic for other ring-chain tautomeric systems involving phenolic OH-group addition to the $C=O$ bond. Equilibria such as **39A** \rightleftharpoons **39B** occur in aqueous solutions of some natural anthocyanins (90CJC755).

Detailed investigations (84TL5813) of 6- and 7-substituted 2-hydroxychromane-4-one **40B** showed that in solution they exist in the three-



component keto-enol and ring-chain equilibria **40A'** \rightleftharpoons **40A** \rightleftharpoons **40B**. The tautomeric ratio depends on the substituent R in the benzene ring, with predominance of cyclic tautomer **40B** (72–97%) in all cases. The introduction of an electron-donating substituent into position 6 increases the nucleophilicity of the phenolic OH group and therefore stabilizes the cyclic

tautomer **40B**. Thus, in CDCl_3 solution for **40** ($\text{R} = \text{H}$), $K_T = [\text{B}]/[\text{A} + \text{A}'] = 8.09$, whereas for **40** ($\text{R} = 6\text{-MeO}$), $K_T = 32.3$.

The photochemical isomerization **41B** \rightarrow **41A** was observed in nonpolar solvents (83AJC1603). Equilibrium ($K_T \sim 1$) was attained in CD_3OD solution after several days, but following concentration and cooling of the solution, only the cyclic isomer **41B**, solvated by methanol, was isolated in the solid state. Alcoholic solvents effectively quench the photochemical isomerization.

The ring-chain equilibrium of *o*-hydroxyphenoxymethyl ketones **42A** \rightleftharpoons **42B** (see Tables VI and VII) and the diastereomeric equilibrium **42B** \rightleftharpoons **42B'** (*Z/E*) were investigated thoroughly by means of $^1\text{H-NMR}$ spectroscopy (85KGS1570; 86KGS472; 88ZOR2167; 89ZOR1273; 91-ZOR1058). As shown in Table VI, substituents ($\text{R}^3 = 2,4,5\text{-}$ and $2,4,6\text{-Me}_3\text{C}_6\text{H}_2$) sterically shielding the $\text{C}=\text{O}$ group stabilize the open-chain tautomer **42A**. The stability of the open-chain tautomer is increased by the introduction of a phenyl ($\text{R}^3 = \text{Ph}$) or a π -electron-rich heteroaryl ($\text{R}^3 = 2\text{-}$

TABLE VI
RING-CHAIN CONSTANTS^a (**42A** \rightleftharpoons **42B** + **42B'**) AND DIASTEREOMERIC (**42B** \rightleftharpoons **42B'**)
EQUILIBRIA FOR *o*-HYDROXYPHENOXYMETHYL KETONES

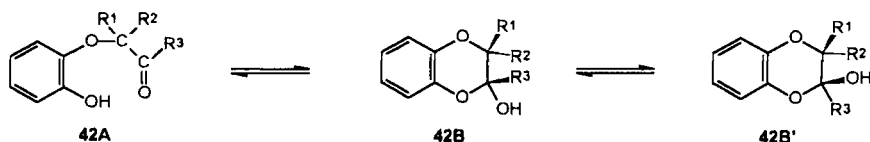
R^1	R^2	R^3	$K_T = [\text{B} + \text{B}']/[\text{A}]$	$K_D = [\text{B}]/[\text{B}']$	<i>Z/E</i>	References
H	H	Me	31.9			<i>b</i>
H	H	<i>t</i> -Bu	7.72			<i>b</i>
H	H	Ph	4.22			<i>b</i>
H	H	2,4,4-Me ₃ C ₆ H ₂	0.36			<i>b</i>
H	H	2,4,6-Me ₃ C ₆ H ₂	0			<i>b</i>
H	H	2-Furyl	0.27			<i>b</i>
H	H	2-Thienyl	0.27			<i>b</i>
H	H	2-Pyridyl	6.40			<i>c</i>
H	H	2-Quinolyl	8.85			<i>c</i>
H	Me	Me	>99	1.86		<i>d</i>
H	Me	4-BrC ₆ H ₄	>99	4.0		<i>d</i>
H	Me	Ph	28.1	3.82		<i>d</i>
H	Me	4-MeOC ₆ H ₄	6.50	3.87		<i>d</i>
H	Me	2-Pyridyl	>99	6.14		<i>c</i>
H	Me	2-Quinolyl	>99	6.23		<i>c</i>
H	Ph	Ph	46.6	15.3		<i>d</i>
H	MeCO	Me	90	5.67		<i>d,e</i>
Me	Me	Me	>99			<i>b</i>
Me	Me	2-Pyridyl	>99			<i>c</i>
Me	Me	2-Quinolyl	>99			<i>c</i>

^a Determined by $^1\text{H-NMR}$ in $(\text{CD}_3)_2\text{CO}$ at 25°C . The data for compounds **42** ($\text{R} = \text{R}^1 = \text{H}$; $\text{R}^2 = \text{XC}_6\text{H}_4$) are not included. See Table VII and Dzvinchuk and Lozinskii (88ZOR2167).

^b Data from (86KGS472). ^c Data from Dzvinchuk *et al.* (91ZOR1058). ^d Data from Dzvinchuk and Lozinskii (91ZOR649). ^e Data from Dzvinchuk and Lozinskii (89ZOR1273).

furyl or 2-thienyl) substituent on the $C=O$ group because of the free-energy gain caused by the conjugation ($Ar-C=O$) in the molecule with the open-chain structure. Dimethyl substitution ($R^1 = R^2 = Me$) strongly stabilizes the cyclic tautomer because of the Thorpe–Ingold effect. The cyclic tautomer is also stabilized by the introduction of only one methyl or phenyl group as the substituent in the connecting link ($R^2 = Me$ or Ph). It has been shown (91ZOR649) that, in the presence of a chiral carbon atom adjacent to the $C=O$ group in the open-chain molecule **42A** ($R^1 \neq R^2$), the three-component equilibrium exists, with the participation of two diastereomers **42B** and **B'**. For all derivatives investigated, the *Z*-diastereomer (**42B**) predominates ($K_D > 1$; see Table VI). This is caused by the nonbonding interaction between the substituents R^2 and R^3 in the cyclic tautomer, destabilizing the *E*-diastereomer **42B'**.

The constants of the equilibrium $42A \rightleftharpoons 42B$ ($R^1 = R^2 = H$; $R^3 =$

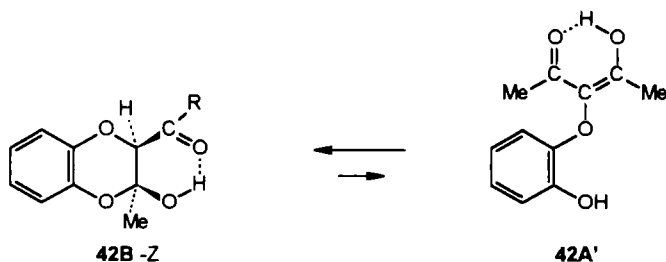


XC_6H_4) were determined (88ZOR2167) by means of 1H -NMR spectroscopy in a large number of different solvents. Primarily for the ring–chain tautomeric system, the influence of the solvent on the equilibrium constant was characterized quantitatively by using the Palm–Koppel (72MI1; 77MI1; 88MI6) equation:

$$\log K_T = \log K_T^0 + yY + pP + eE + bB,$$

where K_T is the ring–chain tautomeric equilibrium constant in the solvent; K_T^0 is equilibrium constant in the gas phase; and y , p , e , and b are regression coefficients characterizing the sensitivity of the tautomeric equilibrium to change in the polarity Y , polarizability P , general acidity E , and general basicity B of the solvent, respectively. The regression analysis was carried out under the assumption that the characteristics Y , P , E , and B of deuterated and nondeuterated solvents do not differ. This assumption was established in part by the fact that the equilibrium constants measured for $CDCl_3$ and $CHCl_3$ solutions at $25^\circ C$ for the tautomeric system investigated are equal. The calculations showed that the influence of the solvent general acidity E can be neglected. The Palm–Koppel equation allows calculation of the ring–chain equilibrium constant in the gas phase (K_T^0), which unfortunately cannot be measured sufficiently accurately by direct experimental methods at present. The large values of the equilibrium constants calculated for the gas phase ($42A \rightleftharpoons 42B$, $R^1 = R^2 = H$, $R^3 = XC_6H_4$; when $X = H$,

4-NO₂, 3-NO₂, 4-Br, 4-Ph, 4-Me, 4-MeCONH, and 4-MeO, $\log K_T^0 = 4.56, 5.06, 4.46, 4.49, 2.08, 4.00, 0.67$ and 2.47 , respectively) show that in solution the open-chain tautomer **42A** is strongly stabilized by solvation effects. An increase in the polarity and polarizability of the solvent shifts the equilibrium toward the open-chain tautomer ($y < 0, p < 0$). The higher polarity of the open-chain tautomer may be caused by intramolecular hydrogen bonds, as shown in **43** or **44**. An increase in the general basicity of the



medium leads to a considerable equilibrium shift in favor of the cyclic tautomer ($b > 0$). For all derivatives **42** investigated, the equilibrium constant K_T is proportional to the increasing proton-acceptor character of the solvent used: acetonitrile < acetone < DMSO < pyridine. Hence, it can be concluded that the OH groups in the tautomers **42A** and **42B** are unequal with respect to their proton-donating ability in the formation of intermolecular hydrogen bonds with solvent molecules. The hemiacetal OH group in **42B** is more favorable, but the phenolic OH group in **42A** is rather strongly bonded intramolecularly, as shown in formulas **43** and **44** and established by means of ¹H-NMR.

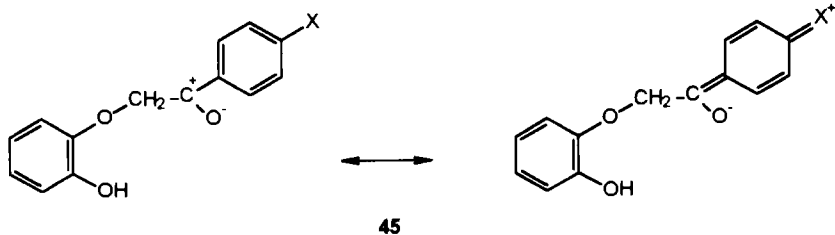
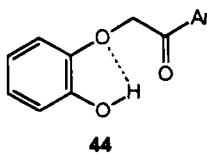
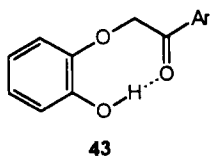


TABLE VII

RING-CHAIN EQUILIBRIUM **42A** \rightleftharpoons **42B** ($R^1 = R^2 = \text{H}$; $R^3 = \text{Ph}$) CONSTANTS FOR VARIOUS SOLVENTS AND THE CORRELATION PARAMETERS FOR THE EQUILIBRIUM **42A** \rightleftharpoons **42B** ($R^1 = R^2 = \text{H}$; $R^3 = \text{XC}_6\text{H}_4$) ACCORDING TO THE YUKAWA-TSUNO EQUATION^a

Parameter	C ₅ D ₅ N	CD ₃ OD	(CD ₃) ₂ SO	(CD ₃) ₂ CO	CD ₃ CN	CHCl ₃	CDCl ₃	HCOOH	C ₅ D ₅ N-H ₂ O (4:1) ^b	(CD ₃) ₂ CO-H ₂ O (4:1) ^b
(<i>K_T</i>) ₀	10.2	6.11	5.43	4.48	2.50	1.54	1.47	0.78	7.44	2.15
<i>r</i> ^c	1.0	1.0	1.0	1.0	0.75	0.50	0.50	0.25	1.0	0.75
ρ	1.07	1.16	1.16	1.20	1.26	1.42	1.43	1.43	1.12	1.32

^a Data from Dzvinchuk and Lozinskii (88ZOR2167). Determined by ¹H-NMR at 25°C (in CHCl₃ at 20°C). The values (*K_T*)₀ were directly measured, rather than obtained from regression analysis. The standard errors of the slope are in the range 0.01–0.03. *n* = 8 (X = H, 3-NO₂, 4-NO₂, 4-Br, 4-Ph, 4-Me, 4-MeCONH, 4-MeO). ^b Molar ratio. ^c This is the coefficient of the Yukawa-Tsuno equation, not the correlation coefficient. The correlation coefficients lie in the range 0.997–0.999.

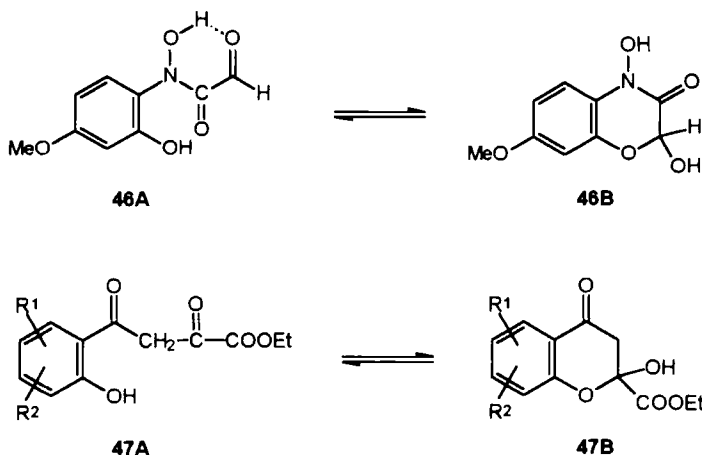
A good correlation was obtained between the equilibrium constants K_T measured in different solvents for the derivatives **42** ($R^1 = R^2 = H$; $R^3 = XC_6H_4$) and the electronic characteristics of the substituent X via the Yukawa-Tsuno equation:

$$\log K_T/(K_T)_0 = \rho[\sigma + r(\sigma^+ - \sigma)] \quad (\text{see Table VII})$$

The data in Table VII reveal that increasing solvent nucleophilicity leads to a decreasing coefficient ρ . The sensitivity of the equilibrium **42A** \rightleftharpoons **42B** to the influence of substituent X is decreased and the role of the polar structure **45** in the stabilization of the open-chain tautomer is increased. Solvation by nucleophilic solvents gives rise to an electron-density enhancement on the C=O group carbon atom, which decreases its intramolecular reactivity toward addition of the nucleophilic OH group. Such solvation is pronounced for compounds **42** with an electron-withdrawing group X in the aryl substituent ($R^2 = XC_6H_4$). The increase of the solvent proton-accepting ability therefore causes a more markedly expressed electronic influence of electron-donating groups X, but quenches the influence of electron-withdrawing groups X on the ring-chain equilibrium (see the changes in coefficient r in Table VII) (88ZOR2167).

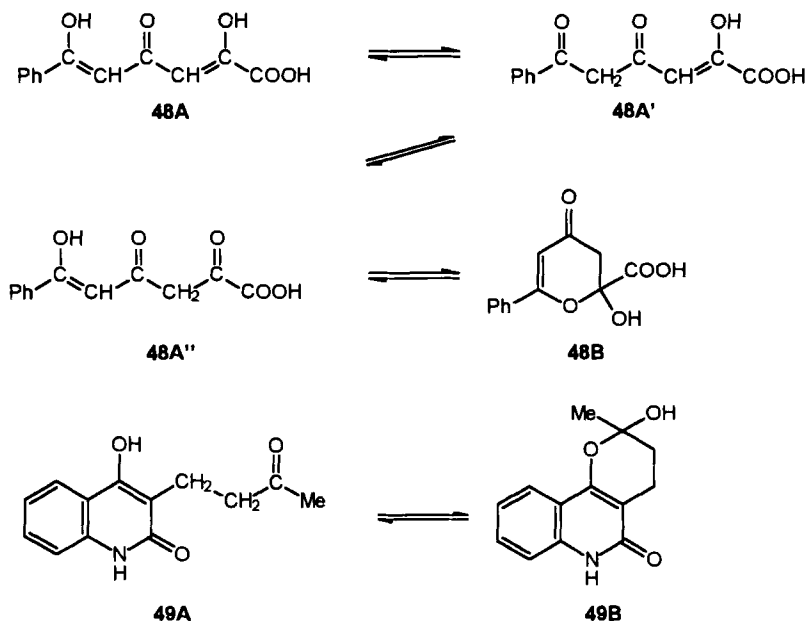
3-Acetyl-2-hydroxy-2-methyl-2,3-dihydrobenzo-1,4-dioxan (**42**, $R^1 = H$; $R^2 = MeCO$; $R^3 = Me$) exists as a mixture of two cyclic diastereomers **42B** and **B'**, both stabilized by an intramolecular hydrogen bond (**42B-Z** and **48-E**). The proportion of the open-chain tautomer **42A'**, also containing an intramolecular hydrogen bond in the enolized pentane-1,3-dione moiety, is very small ($\sim 1\%$) at equilibrium (89ZOR1273).

Extracts of various cereals such as rye, wheat, and maize contain 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (**46B**), which is involved in



the resistance of these plants to pests and pathogens. The decomposition mechanism of **46B** was studied (85T4983) with the aim of interpreting its widespread toxicity at the molecular level. The first step of the two assumed decomposition mechanisms involves the ring-chain equilibrium **46A** \rightleftharpoons **46B**. By means of polarography (86JOC3542), very low concentrations of the open-chain tautomer **46A** were determined quantitatively, which led to the following equilibrium constants: in DMF, $K_T = 480$; in DMSO, $K_T = 1370$; and in pyridine, $K_T = 3700$. Since the open-chain tautomer **46A** is stabilized by an intramolecular hydrogen bond, an increase in the solvent nucleophilicity shifts the equilibrium in favor of the cyclic tautomer **46B**. A linear relationship was found between $\log K_T$ and the donor number of the solvent (78MI2), characterizing its ability to donate an electron pair for formation of an intermolecular hydrogen bond.

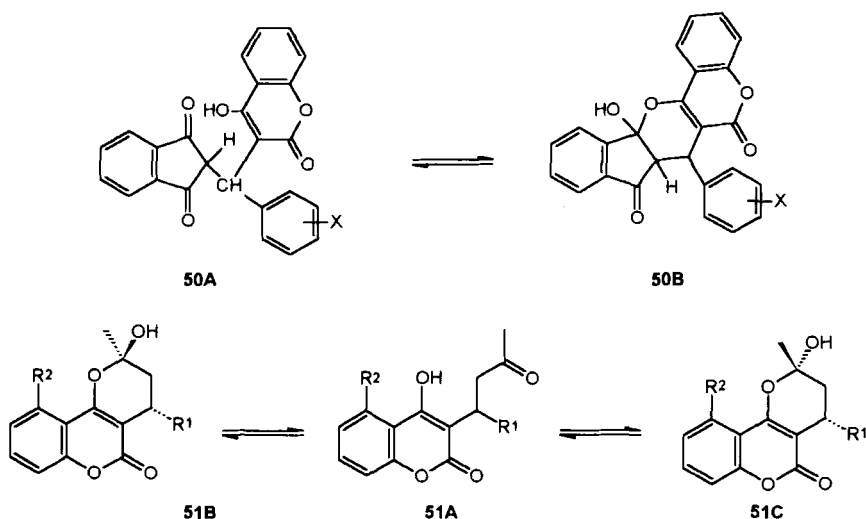
Ethyl chromone-2-carboxylate (**47B**; $R^1 = R^2 = H$) and all its benzo analogs ($R^1, R^2 = 5,6\text{-benzo}, 6,7\text{-benzo}$ and $7,8\text{-benzo}$) were found to be subject to ring-chain tautomerism (**47A** \rightleftharpoons **47B**) (89JHC29). In $CDCl_3$, the 5,6-benzo-fused derivative exhibited only the ring form. The 6,7-benzo-fused compound indicated about 75% of the ring form, while the 7,8-benzo-fused derivative exhibited 40% of the ring tautomer. The unsubstituted compound (**47**, $R^1 = R^2 = H$) indicated about 60% of the cyclized product.



c. *Addition of Enolic OH.* A rather complex four-component tautomeric equilibrium was detected (91JOC4067) by means of ^1H -NMR spectroscopy in solutions of 6-phenyl-2,4,6-trioxohexanoic acid (**48**), which is of current interest because some related compounds have been implicated in the bacterial oxidation of certain polychlorobiphenyls. The acid **48** exists in a very solvent-sensitive tautomeric system. On changing from the solution in $(\text{CD}_3)_2\text{CO}$, which at equilibrium contains 86% of **48A**, ~7% of **48A'**, and small amounts of **48A''** and **48B**, to the solution in $(\text{CD}_3)_2\text{SO}$, the equilibrium ratio of the cyclic tautomer increases dramatically: 52% of **48B**, 42% of **48A**, and 6% of **48A'**.

By ^1H - and ^{13}C -NMR spectroscopy it was shown that the equilibrium **49A** \rightleftharpoons **49B** shifted in favor of the cyclic tautomer (88KPS100) in $(\text{CD}_3)_2\text{SO}$ and $\text{C}_5\text{D}_5\text{N}$ solutions (in both, $K_T \sim 3$). In acidic medium, the open-chain tautomer **49A** predominates ($K_T \sim 0.33$ in CF_3COOH). IR Spectroscopy revealed that in the solid state the compound possesses the cyclic structure **49B**.

The equilibrium **50A** \rightleftharpoons **50B** was observed (83ZSK176) in solution for



2- α -(4-hydroxycoumarin-3-yl)-benzylindane-1,3-dione. In CDCl_3 solution, when $\text{X} = \text{H}$ or 4-Br, $K_T = 0.1$, and when $\text{X} = 2\text{-Cl}$, $K_T = 1.0$ (^1H -NMR).

Warfarin, 3-(1-phenyl-3-oxobutyl)-4-hydroxycoumarin (**51**; $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{H}$), is a clinically useful oral anticoagulant drug, which exists in two diastereomeric cyclic hemiketal forms and as the open-chain ketone (**51B** \rightleftharpoons **51A** \rightleftharpoons **51C**) (84JMC1092; 90MI3). Table VIII shows that the intro-

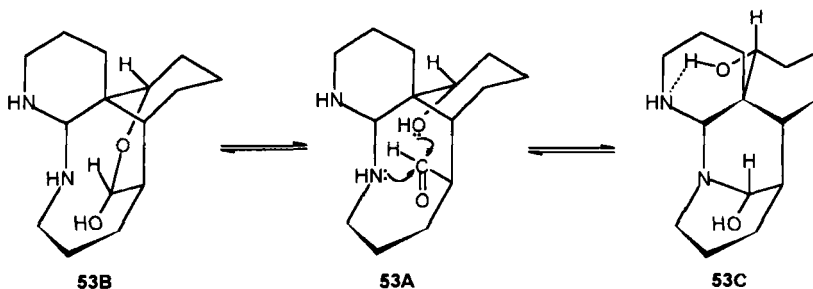
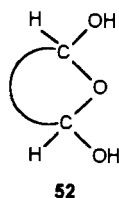
TABLE VIII
EQUILIBRIUM PERCENTAGES FOR WARFARIN
DERIVATIVES **51** IN CDCl_3^a

R^1	R^2	51A (%)	51B (%)	51C (%)
Ph	H	15	45	40
Ph	OH	50	22	28
Me	H	30	35	35
Me	OH	80	5	15

^a Data from Castleberry *et al.* (90MI3). Determined by $^1\text{H-NMR}$ at 27°C .

duction of an OH group at position 5 increases the proportion of the open-chain form **51A** due to the intramolecular hydrogen bond between the *peri* OH groups. X-Ray analyses reveal that 5-hydroxy-warfarin (**51**; $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{OH}$) crystallizes as the open-chain isomer, in contrast with warfarin itself, which occurs as *cis* or *trans* hemiketals (90MI3).

d. *Addition of gem-Diolic OH.* Intramolecular addition of one of the two *gem*-diolic OH groups to the aldehyde $\text{C}=\text{O}$ group leads to the stable cyclic hydrates **52** of *o*-phthalaldehyde [79JCS(P2)642; 90JCS(P2)



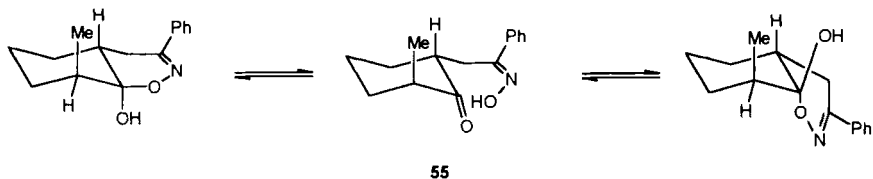
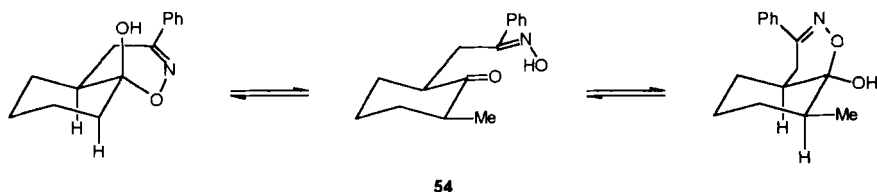
2089], naphthalene-1,8-dicarbaldehyde [63JOC2703], and phenanthrene-4,5-dicarbaldehyde [90JCS(P2)2093]; but biphenyl-2,2'-dicarbaldehyde does not form such a cyclic hydrate [90JCS(P2)2081].

Intramolecular transannular OH-group addition to the C=O bond yields bicyclic hemiacetals of erythromycin [90JCS(P1)1409; 91JCS(P2)1481] and related polyfunctional macrocycles.

An interesting transannular competitive OH- and NH-group addition to the aldehyde C=O group was observed (86KPS730) for the tautomeric system **53B** \rightleftharpoons **53A** \rightleftharpoons **53C** in CDCl₃ solution.

2. Derivatives Containing a N—OH Group

¹H-NMR and ¹³C-NMR spectroscopy demonstrated a three-component equilibrium (83G91) in (CD₃)₂SO solutions of the diastereomeric monooximes of 5-methyl-2-phenacylcyclohexanone **54** and **55**. The same methods revealed the ring-chain equilibrium **56A** \rightleftharpoons **56B** (X = H₂, R = Ph) in solutions of 5-hydroxy-5-methyl-2-phenylisoxazolidines (89KGS823). An increase in the solvent proton-accepting ability shifted the equilibrium in favor of the open-chain tautomer **56A**: in CCl₄, *K*_T = 1.0; and in (CD₃)₂SO,



$K_T = 0.43$. For some derivatives with related structure **56** ($X = O$; $R = Ph$, $PhCH_2$), the equilibrium **56A** \rightleftharpoons **56B** observed (91KGS280) in $(CD_3)_2SO$ solution was entirely shifted toward the cyclic tautomer when the solvent was changed to $CDCl_3$.

C. AMINO ALDEHYDES AND KETONES AND RELATED COMPOUNDS

1. Derivatives Containing an Amino Group on an sp^3 or Aromatic Carbon Atom

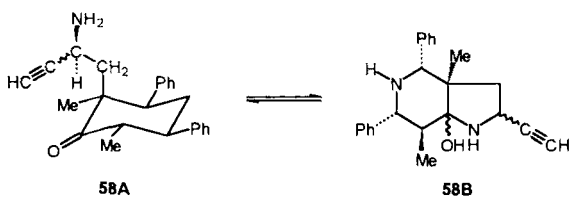
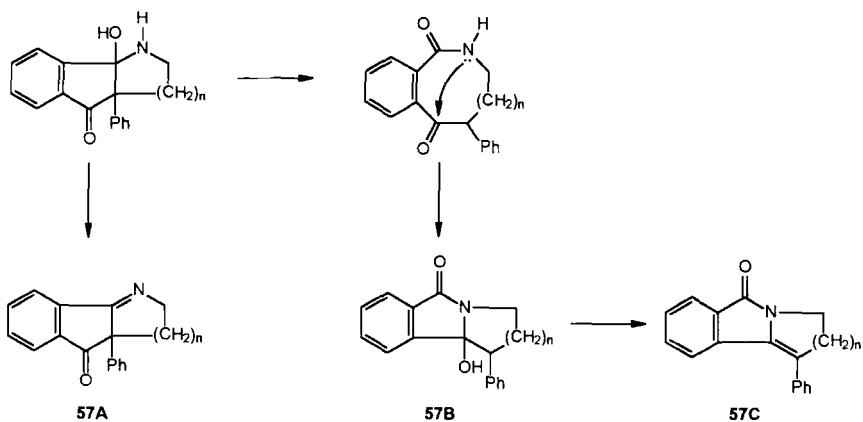
It is presumed [82JCS(P1)2783; 85JCS(P1)191] that intramolecular addition of an NH_2 group to the $C=O$ bond (Scheme 5) precedes the spontaneous rearrangement of 2-(ω -aminoalkyl)-2-phenylindane-1,3-diones formed by hydrazinolysis of the corresponding phthalimidoalkyl derivatives. This rearrangement involves intramolecular NH_2 -group addition to one $C=O$ group, ring expansion proceeding by indane ring opening and subsequent transannular NH group addition to the other $C=O$ group. Depending on the length of the alkyl chain ($n = 1, 2, 3$), the products **57A**, **B**, **C** or their mixtures have been obtained. An analogous recyclization reaction called "crisscross annulation" (84JOC953) has been observed (84CC354) for other cyclic 1,3-diketone derivatives with related structures.

Four diastereomers of 2-ethynyl-7a-hydroxy-3a,7-dimethyl-4,6-diphenylperhydropyrrolo[3,2-*c*]pyridine (**58B**) were recently isolated (92KGS-903). It was established by means of 1H -NOESY and ^{13}C -NMR spectroscopy that the stereochemical differences in the structures of the diastereomers involve *cis* and *trans* fusion of the rings and different configurations at C(2). In solution and in the gas phase, the corresponding ring-chain equilibrium **58A** \rightleftharpoons **58B** was detected, with two open-chain epimers (different configurations at $C-NH_2$).

1H -NMR and ^{13}C -NMR spectroscopy (84TL6063) showed that 1-acetyl-2,3-dihydroxyindolines in $CDCl_3$ solution exhibit the ring-chain equilib-



SCHEME 5



rium $\mathbf{59A} \rightleftharpoons \mathbf{59B}$ ($R^1 = R^3 = \text{Me}$; $R^2 = \text{Me, Ph}$). The benzamide exists as open-chain isomer $\mathbf{59A}$ ($R^1 = \text{Ph}$; $R^2 = R^3 = \text{Me}$), but the cyclohexanone derivative possesses the cyclic structure $\mathbf{59B}$ [$R^1 = \text{Me}$; $R^2, R^3 = -(\text{CH}_2)_4-$].

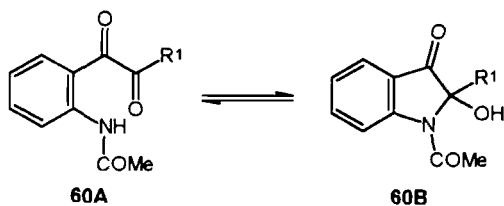


TABLE IX
RING-CHAIN EQUILIBRIUM CONSTANTS FOR 2-HYDROXY INDOLINES
58 AND **59**^a

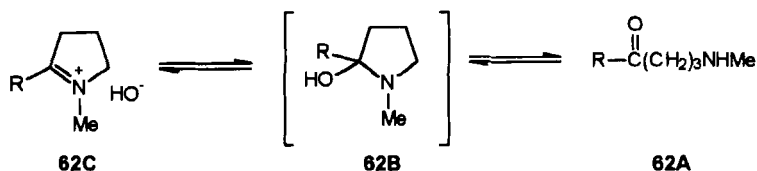
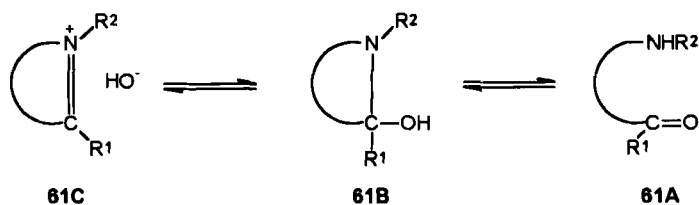
Equilibrium	Solvent	R ¹	R ²	R ³	K _T
58A ⇌ 58B	(CD ₃) ₂ SO	H	—	—	^b
58A ⇌ 58B	(CD ₃) ₂ SO	Me	—	—	^b
58A ⇌ 58B	(CD ₃) ₂ SO	Ph	—	—	^b
58A ⇌ 58B	CDCl ₃	Ph	—	—	0.5
59A ⇌ 59B	(CD ₃) ₂ SO	Me	H	Me	^b
59A ⇌ 59B	(CD ₃) ₂ SO	Me	Me	Me	3
59A ⇌ 59B	CDCl ₃	Me	Me	Me	0.55

^a Data from Kawasaki *et al.* (87CPB1339). ^b Only the ring form is detectable.

Later, Sakamoto *et al.* reexamined the tautomerism of hydroxyindolines **59A** ⇌ **59B** and **60A** and **60B**. It was found that in (CD₃)₂SO the ring form is highly preferred in most cases, whereas in CDCl₃ ring and chain forms can be detected (Table IX).

2. Covalent Hydration of Nitrogen-Containing Heterocycles and Heterocyclic Pseudobases

The tautomeric system aminoaldehyde (or, more rarely, aminoketone) vs. carbinolamine **61A** ⇌ **61B** can be formed by the covalent addition of an OH group to heterocycles containing immonium (*N*-protonated, *N*-alkyl or *N*-aryl) groups. For a review, see Bunting [79AHC(25)1].

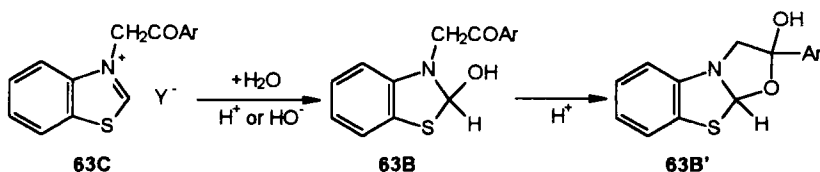


The investigations by Beke and Szántay [61LA(640)127; 63AHC(1)167] led to the conclusion that the equilibria $\mathbf{61C} \rightleftharpoons \mathbf{61B}$ and $\mathbf{61B} \rightleftharpoons \mathbf{61A}$ could not be observed simultaneously in the systems investigated so far. This conclusion was disproved by Brandänge and Rodriguez [see (88TH1) and references therein], who showed that the equilibrium $\mathbf{62C} \rightleftharpoons \mathbf{62A}$ exists at sufficiently high pD values in aqueous (D_2O) solutions of a large number of 1-methylpyrrolinium ions $\mathbf{62C}$ bearing various R substituents. Electron-withdrawing aryl R substituents shift the equilibrium in favor of the open-chain tautomer $\mathbf{62A}$, but electron donors stabilize the pyrrolinium ion $\mathbf{62C}$. When R = H or alkyl, the pyrrolinium form $\mathbf{62C}$ predominates, while in neutral or acidic solution, the open-chain tautomer $\mathbf{62B}$ is almost absent. The concentration of the carbinolamine tautomer $\mathbf{62B}$ is lower than the sensitivity of the ^1H - and ^{13}C -NMR methods used in these investigations.

As a general rule, the introduction of an electron-withdrawing substituent onto the $\text{C}=\text{O}$ group always displaces equilibria such as $\mathbf{62A} \rightleftharpoons \mathbf{62B}$ in favor of the cyclic tautomer (I-246). The opposite electronic influence of the R substituent (88TH1) for the equilibrium $\mathbf{62C} \rightleftharpoons \mathbf{62A}$ appears to be caused by the dominant electronic effect of R in stabilizing the pyrrolinium ion $\mathbf{62C}$, which has an opposite character.

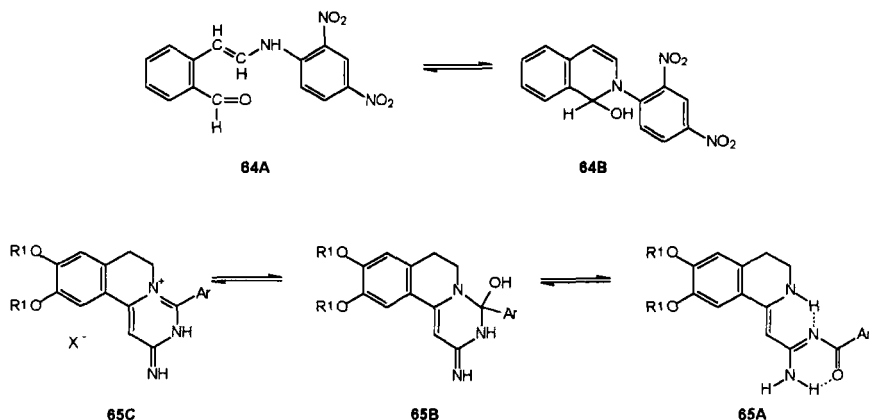
For the 3-pyridyl derivative $\mathbf{62}$ (R = 3-Py), it was demonstrated [83ACS(B)617] that the open-chain tautomer $\mathbf{62A}$ or its form protonated on the pyridine nitrogen predominates at high and low solution pH, whereas the equilibrium concentration of the pyrrolinium ion $\mathbf{62C}$ reaches a maximum (53%) at pH 7. The covalent hydrations of compound $\mathbf{62}$ (R = 3-Py) and 3,4,5,6-tetrahydro-2,3'-bipyridine (anabaseine) were more thoroughly investigated by Zoltewicz (89JOC4462) and all equilibrium constants were measured.

Subsequent hemiacetalization of the OH group was observed [90JIC(B)180] for the 3-phenacylbenzothiazolium cations $\mathbf{63C}$ (Ar = 4-XC₆H₄, X = H, Br, Cl, Me, MeO).



It was presumed (83JA2335; 86JOC2150) that the covalent hydration of the thiazolium ion with reversible ring-opening and ring-closing processes plays an important role in the metabolism of vitamin B₁ (thiamine); these reactions have therefore been thoroughly investigated [88JCS(P2)1409; 89JCS(P2)25; 90JCS(P2)505, 90JCS(P2)1045].

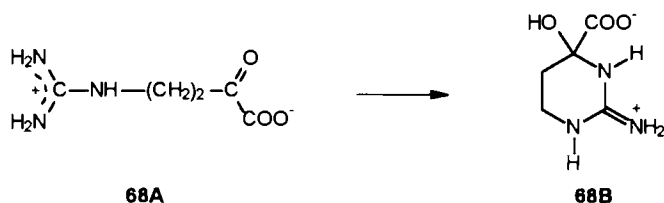
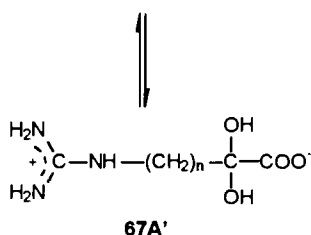
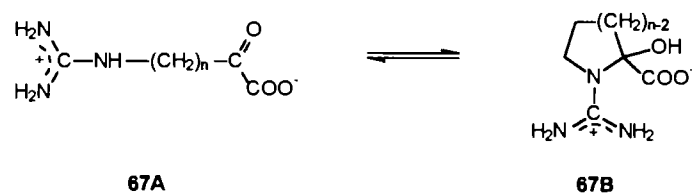
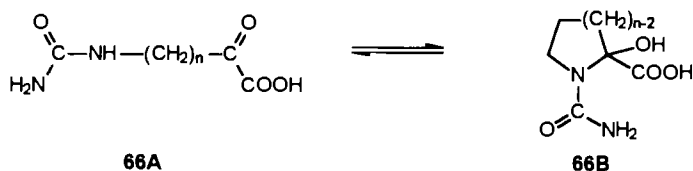
By means of solid-state ^{13}C -NMR spectroscopy (CP/MAS), the structures of both solid isomers **64A** ($\text{C}=\text{O}$ δ = 197.1 ppm) and **64B** [$\text{C}(\text{OH})\text{N}$ δ = 81.4 ppm], first obtained [61LA(640)127] by pseudobase formation of the 2-(2,4-dinitrophenyl)isoquinolinium ion, have been confirmed (84CB702). In hexamethylphosphoric triamide (HMPT) solution, the equilibrium $\text{64A} \rightleftharpoons \text{64B}$ constant was determined (K_T = 9.0) and the *E* conformation of the substituents in the open-chain isomer **64A** was determined.



For 10-dialkoxy-4-aryl-2-imino-6,7-dihydropyrimido[6,1-*a*]isoquinolinium chloride **65C** ($\text{X} = \text{Cl}$), the pH-dependent equilibrium $\text{65C}(\text{X} = \text{OH}) \rightleftharpoons \text{65B} \rightleftharpoons \text{65A}$ was detected (90CB493). The open-chain isomer **65A** was isolated in the solid state, and X-ray diffraction revealed the presence of two intramolecular hydrogen bonds. The two six-membered chelate rings in **65A** stabilize the open-chain isomer. The isomers **65A** are therefore stable in the solid state and in aprotic solvents, but revert to the cations **65C** in dilute protic solvents.

3. Urea, Thiourea, and Guanidine Derivatives

A ring-chain equilibrium displaced in favor of the cyclic tautomer was observed [78JBC(253)5407; 83LA1623] in neutral aqueous solutions of 5-carbamido-**66** ($n = 3$; K_T = 5.67) and 5-guanidino-2-oxovaleric **67** ($n = 3$; K_T = 3.17) acids. In aqueous solutions of acid **67** ($n = 3$), ^1H -NMR spectroscopy detected the presence of 4% of the open-chain tautomer hydrate **67A'** ($n = 3$). In acidic medium, the amount of this hydrate is higher. The dipolar cyclic structure of **67B** ($n = 3$) in the solid state was established on the basis of X-ray diffraction data [83AX(C)1240]. Both isomers **67A** and



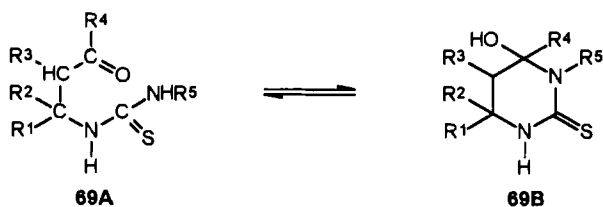
67B ($n = 3$) were isolated in the solid state from aqueous solutions under different conditions: **A** by evaporation of the solution to dryness; **B** by crystallization from an oversaturated solution.

In contrast with data [78JBC(253)5407] on the predominance of the cyclic tautomers **66B** and **67B** ($n = 4$) in solutions of 6-carbamido- and 6-guanidino-2-oxocaproic acids, a more recent investigation (83LA1623) revealed that in neutral aqueous solutions these acids exist as the open-chain tautomers **66A** and **67A** ($n = 4$) with an admixture of the hydrate **67A'** ($n = 4$). The six-membered ring closure is presumably hindered by the unfavorable steric interaction between the planar guanidino or carbamido

group and the adjacent equatorial carboxy group in the ring. For the five-membered ring closure, such a steric interaction is less marked.

In accordance with ^{13}C -NMR data (83LA1623), 4-guanidino-2-oxobutyric acid exists in the solid state and in solution only as the stable cyclic isomer **68B**.

Mass-spectrometric investigation (83KGS1273) showed that the more substituted *N*-(3-oxoalkyl)thioureas **69** ($\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^5 = \text{alkyl, Ar}$) exhibit a ring-chain equilibrium in the gas phase, but the less substituted derivatives **69** ($\text{R}^1 = \text{R}^2 = \text{H}$; $\text{R}^3 = \text{R}^4 = \text{Me}$; $\text{R}^5 = \text{Me, Et, Bu}$) exist only as open-chain isomers. Clear evidence of the stabilizing effect of *gem*-dimethyl substitution on the cyclic form (Thorpe-Ingold effect) was presented for a gas-phase equilibrium. The mass-spectrometric data are rather similar to those obtained for this system in solution, which indicates that this equilibrium depends mainly on structural, rather than solvation, factors.



4. *O*-(3-Oxoalkyl)hydroxylamines

By means of IR and ^1H -NMR spectroscopy, *O*-(3-oxopropyl)-*N*-benzoylhydroxylamine **70** ($\text{R}^1 = \text{PhCO}$; $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{H}$) was shown (73-ABC2201) to exist as the cyclic isomer **70B**. A more recent investigation (85KGS1137) demonstrated that these derivatives actually possess the 3-hydroxyisoxazolidine structure **70B** in nonpolar aprotic solvents [CCl_4 , CDCl_3 and $(\text{CD}_3)_2\text{CO}$], whereas in polar solvents [CD_3OD , $(\text{CD}_3)_2\text{NCDO}$, $(\text{CD}_3)_2\text{SO}$ and $\text{C}_5\text{D}_5\text{N}$] the equilibrium $\mathbf{70A} \rightleftharpoons \mathbf{70B}$ ($\sim 10\text{--}15\%$ of **A**) exists. Such an equilibrium was observed (87KGS1270) in a large series of 2-hydroxyisoxazolidines **70B** ($\text{R}^1 = \text{PhCO}$, $4\text{-NO}_2\text{C}_6\text{H}_4\text{CO}$, $4\text{-BrC}_6\text{H}_4\text{CO}$, $2,4,5\text{-Me}_3\text{C}_6\text{H}_2\text{CO}$; $\text{R}^2 = \text{H, Me}$; $\text{R}^3 = \text{R}^4 = \text{H}$). The open-chain tautomer



is easy to detect via the aldehydic proton ($\delta = 9.7$ ppm) or aldehydic carbon ($\delta = 190$ – 120 ppm) signals in the NMR spectra. On changing from CDCl_3 to more polar solvents, the equilibrium is displaced in favor of the open-chain tautomer.

An equilibrium of the same pattern was recently detected (91KGS280) for *O*-(3-oxoacyl)hydroxylamine **70** ($\text{R}^1 = \text{PhCO}$; $\text{R}^2, \text{R}^3 = \text{O}$; $\text{R}^4 = \text{Me}$) in CDCl_3 ($K_T = 0.11$) and other nonpolar solvents.

5. 3-Oxoalkylhydrazines

Most *N*-(3-oxoalkyl)-*N'*-acylhydrazines in the solid state and in solution exist as cyclic isomers **71B** (84KGS659; 85KGS1238). By mass spectrometry, it was established (86KGS1334) that for some of these compounds the open-chain tautomer **71A** ($\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$; and $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{PhCH}_2$; $\text{R}^3 = \text{Me}$; $\text{R}^4 = \text{R}^5 = \text{H}$) predominates in the gas phase. ^1H -NMR spectroscopy on solutions of pyrazolidine **71B** ($\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{PhCH}_2$; $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$) in polar solvents ($(\text{CD}_3)_2\text{SO}$, CD_3OD) detected the ring-chain equilibrium (83KGS1422), with $\sim 10\%$ of **71A**. From a more thorough investigation (90KGS1199), it followed that all pyrazolidines **71B** ($\text{R}^1 = 4\text{-XC}_6\text{H}_4$, $\text{X} = \text{H}, \text{Br}, \text{NO}_2, \text{Me}, \text{MeO}$; $\text{R}^2 = \text{PhCH}_2$; $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{H}$) exhibit the equilibrium **71A** \rightleftharpoons **71B**, which is displaced in favor of the cyclic tautomer in $(\text{CD}_3)_2\text{SO}$ solutions. Introduction of an electron-donating substituent on the benzoyl group ($\text{X} = \text{MeO}$) increases the amount of the open-chain tautomer ($\sim 20\%$) at equilibrium. The mass-spectrometric data indicate that the open-chain tautomer content reaches 50% in the gas phase.

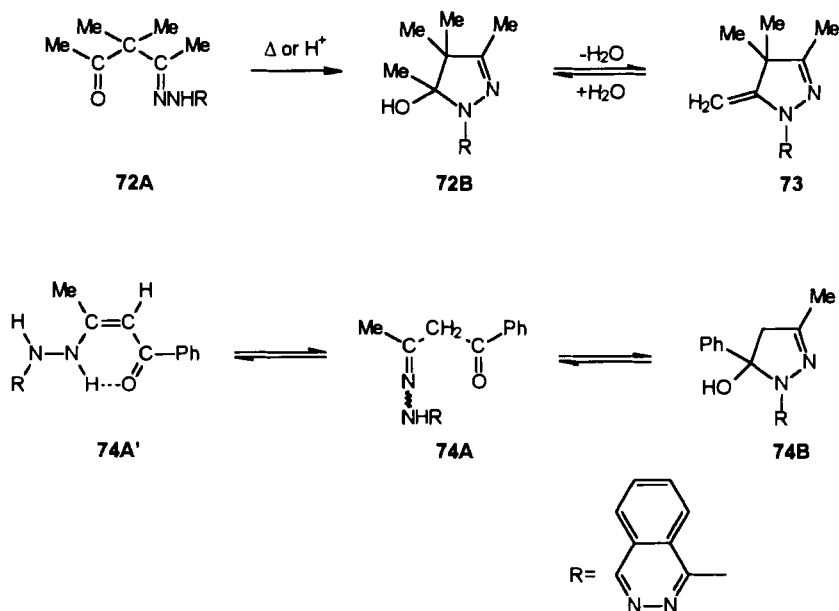


An equilibrium of similar pattern was recently observed (91KGS280) for solutions of the isoxazolidin-5-ones **71B** ($\text{R}^1 = \text{PhCO}$, PhCH_2CO ; $\text{R}^2 = i\text{-Pr}$; $\text{R}^3, \text{R}^4 = \text{O}$; $\text{R}^5 = \text{Me}$) in CDCl_3 and other nonpolar solvents (when $\text{R}^1 = \text{PhCO}$, $K_T = 0.11$; when $\text{R}^1 = \text{PhCH}_2\text{CO}$, $K_T = 0.05$ in CDCl_3). The equilibrium **71A** \rightleftharpoons **71B** for the above-mentioned derivatives in $(\text{CD}_3)_2\text{SO}$ solution is fully shifted toward the open-chain tautomer.

6. Monohydrazones of 1,3-Diketones and Related Compounds

The reactions of 1,3-dicarbonyl compounds with hydrazines comprise one of the most important methods of pyrazole synthesis. Investigations of the mechanisms of these ring-formation reactions by ^1H -NMR spectroscopy and the stopped-flow technique have revealed the intermediates (81ZOR886; 82ZOR909; 84MI7, 84ZOR1494), between some of which a ring-chain equilibrium exists. The great potential of ^{13}C -NMR spectroscopy has been demonstrated [87JCS(P2)969, 87T5171] in this field.

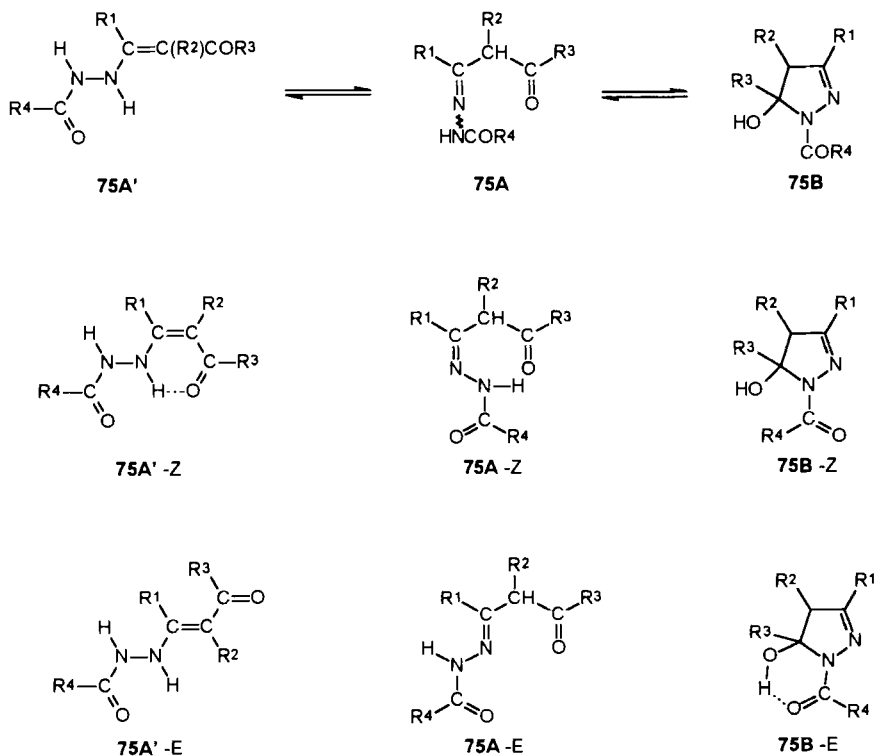
It may be presumed that the ring-chain equilibrium involving formation of a cyclic tautomer by intramolecular addition of a hydrazone NH group to a $\text{C}=\text{O}$ bond in the molecule of a 1,3-diketone monohydrazone would be easy to observe when structural factors prevent or hinder the thermodynamically favored formation of the pyrazole ring. This aim can generally be achieved in various ways. The hydrazones of 2,2-disubstituted 1,3-diketones are derivatives incapable of forming the pyrazole ring. In the reactions of 3,3-dimethylpentane-2,4-dione with monosubstituted hydrazines, the open-chain isomers **72A** [$\text{R} = \text{Me}, i\text{-Pr}, \text{Ph}, 2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3$] were obtained (86ZOR1096; 88ZOR426), but these readily underwent ring closure and subsequent dehydration **72A** \rightarrow **73**. The methylenepyrazolines **73** form the cyclic isomers **72B** after water addition. Only **72B** [$\text{R} = 2,4$ -



(NO₂)₂C₆H₃] is stable in solution; the other hydroxypyrazolines **72B** revert to **73** in several solvents, which prevents investigation of the equilibrium **72A** \rightleftharpoons **72B**. By means of ¹H- and ¹³C-NMR spectroscopy, a three-component equilibrium **74A'** \rightleftharpoons **74A** \rightleftharpoons **74B** was observed (83JHC1231). Measurements in CDCl₃ indicated 31% of **A**, 25.2% of **A'**, and 43.8% of **B**; and in (CD₃)₂SO, 52.5% of **A**, 22% of **A'**, and 25.5% of **B**.

Yakimovich and co-workers (for reviews, see 84MI1; 88MI1) have shown that a pyrazole synthesis can be stopped at the stage of monohydrazone **75A** or cyclic isomer **75B** formation by introducing an acyl group on the hydrazine nitrogen atom. The electron-withdrawing acyl group decreases the nucleophilicity of the nitrogen atom and therefore hinders the ring closure **75A** \rightarrow **75B**. Furthermore, the acyl group hinders the insertion of the nitrogen atom lone-pair electrons into the pyrazole aromatic ring system (2*p* + 4*π*), thereby increasing the activation energy of the reaction **75B** \rightarrow 1-acylpyrazole.

N-Acylhydrazones of 1,3-dicarbonyl compounds can exist in three tautomeric forms: enhydrazone **75A'**, hydrazone **75A**, and 5-hydroxypyrazoline **75B**



75B. Actually, these tautomeric equilibria are more complex because each of these three forms can exist as two geometric isomers (*E* and *Z* for **75A'** and **75A**) or two conformers (rotamers *E* and *Z* for **75B**). When $R^2 \neq H$, two diastereomers (*cis* and *trans* R^2 and R^3) are possible for the cyclic tautomer **75B**. These equilibria have been thoroughly investigated (88TH2) by means of electronic, IR, 1H -, and ^{13}C -NMR spectroscopy. The structure of the solid 5-hydroxypyrazoline **74B-E** ($R^1 = Me$; $R^2 = H$; $R^3 = Ph$; $R^4 = i\text{-}Pr$) was confirmed by X-ray diffraction (87MI5). An approximate generalization of the influence of the structural factor on these equilibria is shown in Table X.

Aroylhydrazones of β -ketoesters exhibit the equilibrium **75A** \rightleftharpoons **75A'** ($R^3 = O\text{-alkyl}$) (79ZOR922). *N*-Aroyl- and *N*-alkanoylhydrazones of pentane-2,4-dione in the solid state and in $CDCl_3$, CD_3OD , benzene, or pyridine solutions exist as the cyclic tautomer **75B-E** ($R^1 = R^3 = Me$; $R^2 = H$) stabilized by an intramolecular hydrogen bond (80ZOR415; 87ZOR1433). For the *N*-aroyl derivatives **75** ($R^1 = R^3 = Me$; $R^2 = H$; $R^4 = XC_6H_4$) in $(CD_3)_2SO$ solution, the equilibrium **75A'** \rightleftharpoons **75B** was observed, but the amount of the enhydrazine tautomer **75A'** does not exceed 5%. On changing from electron-donating substituents X in the aroyl group ($R^4 = XC_6H_4$) to electron-withdrawing substituents, the content of the enhydrazine tautomer **75A'** slightly decreases. Introducing a sterically demanding substituent onto

TABLE X
GENERALIZATION^a OF THE INFLUENCE OF STRUCTURAL FACTORS ON
EQUILIBRIA **75A'** \rightleftharpoons **75A** \rightleftharpoons **75B**

Change in structural factors		Stabilizing (+) or destabilizing (-) effect on tautomers		
		A'	A	B
Increasing steric demands of substituent	R^1	-	-	+
	R^2	-	-	+
	R^3	+	+	-
	R^4	+	-	-
Increasing electron- withdrawing effect of substituent	R^1	-	+	-
	R^3	+	-	+
	R^4	-	+	+

^a Based on the results of investigations of Yakimovich (81ZOR 284; 82ZOR762; 83ZOR880, 83ZOR2333; 84MI1, 84ZOR1371; 85ZOR2493; 86ZOR286; 87ZOR1433; 88MI1, 88TH2; 91ZOR959; 93ZOR905).

the *N*-acyl group ($R^4 = t\text{-Bu}$) increases the content of the enhydrazine form **75A'** ($\sim 10\%$).

A significant stabilization of the cyclic tautomer **75B** was detected after the introduction of an alkyl substituent at position 3 of pentane-2,4-dione ($R^2 = \text{alkyl}$). For these derivatives, the cyclic tautomer **75B** exists as an equilibrium mixture of two diastereomers. An increase in the steric bulk of the substituents R^2 , R^3 , and R^4 displaces the equilibrium in favor of the diastereomer with the *trans* arrangement of the substituents R^2 and R^3 (87ZOR1433).

The influence of the electronic effects of the substituents on the equilibrium **75A'** \rightleftharpoons **75B** was investigated in the series of 1-arylbutane-1,3-dione *N*-aroylhydrazones **75** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = \text{XC}_6\text{H}_4$; $R^4 = \text{YC}_6\text{H}_4$) (82ZOR762). Benzoylacetone *N*-benzoylhydrazone **75** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = R^4 = \text{Ph}$) was isolated as both isomers in the solid state: the yellow form **75B** by crystallization from benzene, and the colorless form **75A'**-*Z*, stabilized by an intramolecular hydrogen bond, by crystallization from hexane. In CDCl_3 solution, full isomerization **75A'**-*Z* \rightarrow **75B** takes place in several hours. In $(\text{CD}_3)_2\text{SO}$ solution, the equilibrium **75A'**-*Z* \rightleftharpoons **75A'**-*E* \rightleftharpoons **75B**-*E* occurs, with a tautomer ratio identical to that for the isomers initially dissolved.

Introduction of an electron-withdrawing substituent Y into the aroyl group on the nitrogen atom shifts the equilibrium **75A'** \rightleftharpoons **75B** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = \text{Ph}$; $R^4 = \text{YC}_6\text{H}_4$) in favor of the cyclic tautomer (Table XI). A good linear correlation has been observed:

$$\log K_T = -0.41 + 0.51\sigma; \quad n = 7; \quad r = 0.99; \quad s_0 = 0.03; \quad s_p = 0.02.$$

It was presumed (82ZOR762; 85ZOR2493) that this influence of electron-withdrawing substituents is determined by the increased stability of the cyclic isomer due to the extended π -*p*- π conjugation ($\text{C}=\text{N}$ bond to nitrogen atom lone-pair electron to $\text{C}=\text{O}$ bond) in the molecule of **75B**. The same stabilization also seems possible in the hydrazone tautomer **75A**, but this has not been detected at all. This apparent contradiction is explained by the fact that insertion of the second nitrogen atom into the rather rigid pyrazoline five-membered ring fixes the planar arrangement of the fragment $\text{C}=\text{N}-\text{N}-\text{C}=\text{O}$, creating more favorable conditions for the conjugation than in the open-chain hydrazone tautomer **75A**.

Introduction of an electron-withdrawing substituent X onto the aroyl group of aroylacetone *N*-benzoylhydrazone **75** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = \text{XC}_6\text{H}_4$; $R^4 = \text{Ph}$), as anticipated, shifts the equilibrium toward the cyclic tautomer:

$$\log K_T = -0.51 + 0.85\sigma; \quad n = 7; \quad r = 0.98; \quad s_0 = 0.09; \quad s_p = 0.08.$$

TABLE XI
RING-CHAIN EQUILIBRIUM CONSTANTS^a FOR
AROYLACETONE AROYLHYDRAZONES
75A' \rightleftharpoons **75B** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = \text{XC}_6\text{H}_4$; $R^4 = \text{YC}_6\text{H}_4$)

X	Y	$K_T = [\text{B}]/[\text{A}' - E + \text{A}' - Z]$
H	4-Me ₂ N	0.14
H	4-MeO	0.30
H	4-Me	0.35
H	H	0.41
H	4-Cl	0.54
H	3-Br	0.56
H	4-NO ₂	1.00
4-Me ₂ N	H	0.06
4-MeO	H	0.14
4-Me	H	0.19
4-Br	H	0.64
3-NO ₂	H	1.17
4-NO ₂	H	1.27
4-Me ₂ N	4-NO ₂	0.15
4-NO ₂	4-Me ₂ N	0.89
4-NO ₂	4-NO ₂	3.76

^a Data from Yakimovich *et al.* (82ZOR762). Determined by ¹H-NMR in 10% solutions in (CD₃)₂SO at 30°C. The ratio of the geometric isomers **75A'**-*E* and *Z* is constant for all derivatives of the series; when X = H, *E/Z* is ~1:19, and when Y = H, *E/Z* is ~1:13.

For all series (see Table XI), a good two-parameter correlation was obtained:

$$\begin{aligned}\log K_T/(K_T)_0 &= \rho_X \sigma_X + \rho_Y \sigma_Y + \alpha \sigma_X \rho_Y; & n &= 16; \\ \log(K_T)_0 &= -0.42 \pm 0.02; \\ \rho_X &= 0.88 \pm 0.05; & \rho_Y &= 0.48 \pm 0.05; \\ \alpha &= 0.06 \pm 0.03; & s_0 &= 0.08.\end{aligned}$$

The small value of the coefficient α and the similar values of ρ_X and ρ_Y in the one- and two-parameter equations indicate that the substituents X and Y exert independent effects on the ring-chain equilibrium.

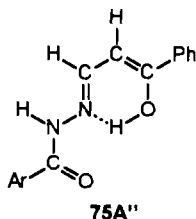
With one exception, *N*-alkanoylhydrazones of benzoylacetone exist in the solid state and in CDCl₃ solution in the cyclic form **75B** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = \text{Ph}$; $R^4 = \text{H, Me, Et, } i\text{-Pr}$) (83ZOR2333). The *N*-pivaloyl derivative **75** ($R^4 = t\text{-Bu}$), the exception in this series, possesses the enhydrazine **75A'**-*Z* structure in the solid state, but in CDCl₃ solution the equilibrium **75A'**-*Z* \rightleftharpoons **75B** ($K_T = 6.7$) exists. By means of ¹H-NMR spec-

troscopy, a signal ($\delta = 4.10$ ppm) with a short lifetime was observed during this equilibration, which may be attributed to the intermediate with the hydrazone structure **75A**. The rates of formation (**75A'** \rightarrow **75A**) and disappearance (**75A** \rightarrow **75B**) of this derivative **75** ($R^4 = t\text{-Bu}$) are rather similar; therefore, this intermediate may be detected. This is clearly not the case for other derivatives of this series because the rate of further transformation of the intermediate is faster than that of its formation. In $(\text{CD}_3)_2\text{SO}$ solution, 1-formylpyrazoline **75B** ($R^1 = \text{Me}$; $R^2 = R^4 = \text{H}$; $R^3 = \text{Ph}$) retains its cyclic structure, but other *N*-alkanoyl derivatives of this series exhibit the equilibrium **75A'**-Z \rightleftharpoons **75B** (when $R^4 = \text{Me}$, $K_T = 6.69$; when $R^4 = \text{Et}$, $K_T = 5.67$; when $R^4 = i\text{-Pr}$, $K_T = 3.61$; and when $R^4 = t\text{-Bu}$, $K_T = 0.07$). Also in this series, it is obvious that an increase in the steric demands of the substituent R^4 displaces the equilibrium in favor of the enhydrazine tautomer **75A'**-Z (83ZOR2333).

Aroylacetaldehyde *N*-aroylhydrazones **75** ($R^1 = R^2 = \text{H}$; $R^3 = \text{XC}_6\text{H}_4$; $R^4 = \text{YC}_6\text{H}_4$) exist in the solid state as the enhydrazines **75A'**-E, whereas in CDCl_3 solution they exhibit the equilibria **75A'**-Z \rightleftharpoons **75A'**-E \rightleftharpoons **75B** (the **75A'**-E form disappears entirely). In pyridine solution, the number of components at equilibrium is higher: **75A'**-E \rightleftharpoons **75A'**-Z \rightleftharpoons **75A'**-E \rightleftharpoons **75B**, this equilibrium being shifted in favor of the enhydrazines **75A'**-E and Z (83ZOR880; 93ZOR905). It was observed qualitatively that introducing an electron-withdrawing substituent Y onto the aroyl group on the nitrogen atom ($R^4 = \text{YC}_6\text{H}_4$) destabilizes the enhydrazine tautomer **75A'** and displaces the equilibrium mostly toward pyrazoline **75B** and slightly toward hydrazone **75A**. The electronic influence of the substituent X on the aroyl group $R^3 = \text{XC}_6\text{H}_4$ is more pronounced. Electron-withdrawing substituents X increase the amount of pyrazoline **75A'** and, to a smaller extent, enhydrazines **75A'**-E and Z, but decrease the amount of hydrazone **75A** at equilibrium. In $(\text{CD}_3)_2\text{SO}$ solution, only the tautomers with open-chain structures predominate in the equilibria **75A'**-E \rightleftharpoons **75A'**-Z \rightleftharpoons **75A'**-E. Small amounts of the cyclic pyrazoline tautomer were detected only for derivatives containing strongly electron-withdrawing substituents X. Electron-withdrawing substituents Y on the *N*-aroyl group shift the equilibria **75A'**-E \rightleftharpoons **75A'**-Z \rightleftharpoons **75A'**-E [$(\text{CD}_3)_2\text{SO}$] slightly in favor of the hydrazone tautomer: $\log K = \log [\text{A}']/[\text{A}] = 0.96 - 0.16\sigma$; $n = 10$; $r = 0.96$. However, electron-withdrawing substituents X ($R = \text{XC}_6\text{H}_4$) act in the opposite direction: $\log K = \log [\text{A}']/[\text{A}] = 0.99 + 0.76\sigma$; $n = 5$; $r = 0.99$ (93ZOR905).

By changing the reaction conditions, Rateb *et al.* [78ZN(B)1527] isolated two groups of *N*-aroyl- and *N*-phenylacetylhydrazones of benzoylacetaldehyde **75** ($R^1 = R^2 = \text{H}$; $R^3 = \text{Ph}$; $R^4 = \text{PhCH}_2$, 4- XC_6H_4 , X = H, Me, MeO, Cl, Br, NO_2), to which they attributed the pyrazoline structure **75B** and

the open-chain *Z*-enol-*E*-hydrazone structure **75A''**. Yakimovich and co-workers confirmed the cyclic structure **75B**, but on the basis of the spectral data in [78ZN(B)1527] and (83ZOR880) they demonstrated (88TH2) that the structure of the second group of the isomers is not **75A''**, but **75A'-E**.



N-Alkanoylhydrazones of benzoylacetaldehyde exist as several isomers in the solid state, depending on the structure of substituent R^4 (83-ZOR2333). When $R^4 = H$, it is **75B** ($R^1 = R^2 = H$; $R^3 = Ph$); when $R^4 = Me$, Et, and Pr, it is **75A-E**; and when $R^4 = t\text{-Bu}$, it is **75A'-E**. In $(CD_3)_2SO$ solution, up to five-component equilibrium mixtures appear, containing hydrazone **75A-E** (two conformers with respect to the hindered rotation around the $CO-N$ bond), enhydrazine **75A'-E** and *Z*, and pyrazoline **75B** tautomers. An increase in the steric bulk of substituent R^4 increases the amount of the enhydrazine tautomer **75A'**. The steric demands of the substituent R^4 are mostly expressed for the pyrazoline tautomer **75B**, which does not form at all when $R^4 = t\text{-Bu}$.

The *N*-benzoylhydrazones of acylpinacolines **75** ($R^1 = \text{alkyl}$; $R^2 = H$; $R^3 = t\text{-Bu}$; $R^4 = Ph$) in solution form equilibria involving the participation of two hydrazone (**75A-E** and *Z*) tautomers, one or two enhydrazine (**75A'-E** and *Z*) tautomers, and one cyclic (**75B**) tautomers (84ZOR1371). Here, clear evidence is presented characterizing the influence of the steric effect of the substituent on the $C=N$ bond: an increase in the steric demands in the series $R^1 = H < Me < i\text{-Pr} < t\text{-Bu}$ shifts the equilibrium toward the cyclic tautomer **75B**. When $R^1 = H$, this tautomer is absent; but when $R^1 = t\text{-Bu}$, the equilibrium is shifted entirely in favor of **75B**.

The change from $CDCl_3$ to C_5D_5N and further to $(CD_3)_2SO$ as solvent stabilizes the hydrazone **75A**, and especially the enhydrazine **75A'**, because these tautomers have a greater tendency to form intermolecular hydrogen-bonds ($N-H \cdots \text{solvent}$) than does the pyrazoline tautomer **75B**, where the OH group ($O-H \cdots \text{solvent}$) is shielded by the sterically demanding substituent $R^3 = t\text{-Bu}$.

Introduction of electron-withdrawing substituents onto the C=N bond in **75A** ($R^1 = \text{COOMe}$, CHF_2 , CF_3) favors the hydrazone tautomer **75A** and leads to the complete disappearance of enhydrazine tautomers **75A'**-*E* and *Z*.

The *N*-benzoylhydrazones of symmetrically substituted 1,3-diketones **75** ($R^1 = R^3 = \text{Me}$, *Et*, *i*-Pr, *t*-Bu; $R^2 = \text{H}$; $R^4 = \text{Ph}$) in CDCl_3 , $\text{C}_5\text{D}_5\text{N}$, and $(\text{CD}_3)_2\text{SO}$ solutions exhibit almost total pyrazoline tautomer **75B** predominance. In $(\text{CD}_3)_2\text{SO}$, the equilibrium $\text{75A}' \rightleftharpoons \text{75B}$ was detected: when $R^1 = R^3 = \text{Me}$, $K_T = 19$; when $R^1 = R^3 = t\text{-Bu}$, $K_T = 10.1$.

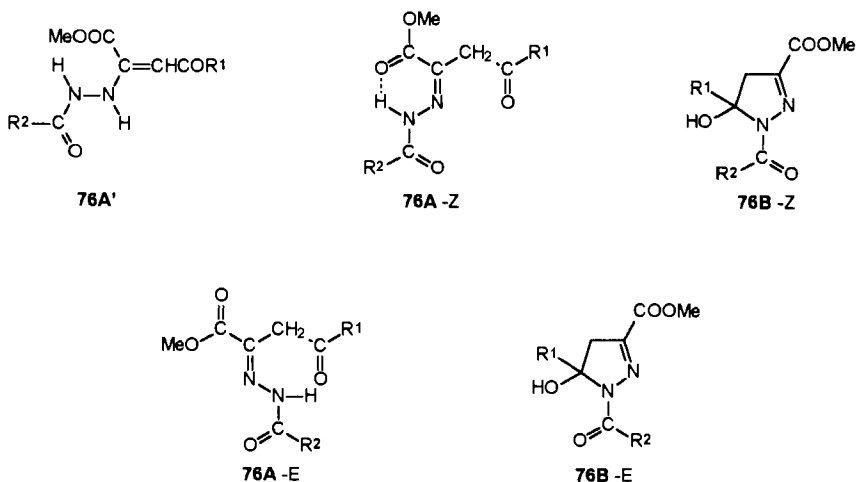
The *N*-alkanoylhydrazones of formylpinacolone **75** ($R^1 = R^2 = \text{H}$; $R^3 = t\text{-Bu}$; $R^4 = \text{H}$, *Me*, *Et*, *i*-Pr, *t*-Bu) in the solid state possess several isomeric structures, depending on the substituent R^4 : **75B** ($R^4 = \text{H}$), **75A'** ($R^4 = \text{Me}$), and mixtures of **75A** + **75A'**-*E* ($R^4 = \text{Et}$, *i*-Pr, *t*-Bu). Increasing the steric demands of the substituent R^4 and/or of the proton-accepting ability of the solvent shifts the equilibrium in favor of the open-chain tautomers **75A** and **75A'**, the cyclic tautomer disappearing entirely when $R^4 = t\text{-Bu}$ (91ZOR959). The *N*-aroylhydrazones of formylpinacolone **75** ($R^1 = R^2 = \text{H}$; $R^3 = t\text{-Bu}$; $R^4 = \text{XC}_6\text{H}_4$) exhibit equilibria only between the open-chain tautomers **75A**-*E* and **75A'**-*Z* in solutions. Electron-withdrawing substituents X favor the hydrazone tautomer **75A**.

The *N*-aroylhydrazones of acetylpinacolone **75** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = t\text{-Bu}$; $R^4 = \text{XC}_6\text{H}_4$) exhibit the four-component equilibrium $\text{75A}-Z \rightleftharpoons \text{75A}'-E \rightleftharpoons \text{75A}'-Z \rightleftharpoons \text{75B}-E$ in CDCl_3 solution, with predominance of the pyrazoline tautomer **75B**-*E*. In $(\text{CD}_3)_2\text{SO}$ solution, a five-component equilibrium was observed (80ZOR2235; 85ZOR2493), the tautomer **75A'**-*E* also being present; but in this solvent the equilibrium is reversed, with a strong predominance of the open-chain tautomers, especially **75A'**. Electron-withdrawing substituents X ($R^4 = \text{XC}_6\text{H}_4$) stabilize the cyclic tautomer **75B**.

The *N*-alkanoylhydrazones of acetylpinacolone **75** ($R^1 = \text{Me}$; $R^2 = \text{H}$; $R^3 = t\text{-Bu}$; $R^4 = \text{H}$, *Me*, *Et*, *i*-Pr) in the solid state and in CDCl_3 solution exist solely as the pyrazoline tautomers **75B**. The *N*-pivaloyl derivative **75** ($R^4 = t\text{-Bu}$) in the solid state possesses the enhydrazine structure **75A'**-*Z*, but its solution in CDCl_3 contains 18% **75A**-*E*, 7% of **75A**-*Z*, 29% of **75A**-*Z*, and 44% of **75B**. In a CDCl_3 solution of the *N*-formyl derivative **75** ($R^4 = \text{H}$), a six-component equilibrium containing the tautomers **75A'**-*E* and *Z*, **75B**-*E* and *Z*, and **75B**-*E* and *Z* has been detected by means of ^1H -NMR spectroscopy (85ZOR2493).

As mentioned previously (84ZOR1371), the introduction of a strongly electron-withdrawing substituent onto the C=N bond (R^1 in **75**) stabilizes the hydrazone tautomer **75A** and leads to the total disappearance of tautomer **75A'** from the equilibrium. This was repeatedly confirmed by investiga-

tion of the *N*-alkanoyl- and *N*-aroylhydrazones of methyl 5,5-dimethyl-2,4-dioxohexanoate **76** ($R^1 = t\text{-Bu}$; $R^2 = \text{alkyl}$, 4- XC_6H_4) (79ZOR1100; 86ZOR286) and the *N*-benzoylhydrazones of methyl 4-aryl-2,4-dioxobutanoates **76** ($R^1 = \text{XC}_6\text{H}_4$; $R^2 = \text{Ph}$) (81ZOR284).



The *N*-aroylhydrazones **76** ($R^1 = t\text{-Bu}$; $R^2 = 4\text{-XC}_6\text{H}_4$), which exist in the solid state as the open-chain isomers³ **76A-E**, slowly (during several days) attain the equilibrium $\text{76A-E} \rightleftharpoons \text{76A-Z} \rightleftharpoons \text{76B}$ in CDCl_3 . The hydrazone **76A-Z** is stabilized by an intramolecular hydrogen bond. As shown in Table XII, electron-withdrawing substituents X shift the equilibrium slightly toward the cyclic tautomer **76B**. The *N*-formylhydrazone possesses the cyclic structure **76B-E** and Z ($R^1 = t\text{-Bu}$; $R^2 = \text{H}$) in the solid state and in CDCl_3 solution. The *N*-alkanoylhydrazones **76** ($R^1 = t\text{-Bu}$; $R^2 = \text{alkyl}$), which exist in the solid state as open-chain isomers **76A-E**, exhibit in CDCl_3 solution the equilibrium $\text{76A-Z} \rightleftharpoons \text{76A-E} \rightleftharpoons \text{76B}$, shifted toward the pyrazoline tautomer **76B**. An increase in the steric demands of the substituent, $R^2 = \text{Me} < \text{Et} < i\text{-Pr} < t\text{-Bu}$, displaces the equilibrium in favor of the open-chain tautomers **76A-E** and Z (see Table XII), with the amount of the Z-isomer showing the main increase. In the proton-accepting solvents $\text{C}_5\text{D}_5\text{N}$ and $(\text{CD}_3)_2\text{SO}$, which usually stabilize the enhydrazine tautomer of the system **75**, form **76A** could not be detected at all by $^1\text{H-NMR}$ spectroscopy (86ZOR286).

³ It should be noted that, after the introduction of a COOMe group at the $\text{C}=\text{N}$ bond in **76A**, the designation of the conformations *E* and *Z* has been reversed on comparison with those of hydrazones **75A**.

TABLE XII
RING-CHAIN EQUILIBRIUM **76A** \rightleftharpoons **76B**
($R^1 = t\text{-Bu}$) CONSTANTS^a

R^2	$K_T = [\mathbf{B}]/[\mathbf{A} - E + \mathbf{A} - Z]$
4-Me ₂ NC ₆ H ₄	0.09
4-MeOC ₆ H ₄	0.11
4-MeC ₆ H ₄	0.11
Ph	0.14
4-BrC ₆ H ₄	0.20
4-NO ₂ C ₆ H ₄	0.31
H	>99
Me	3.0
Et	2.23
i-Pr	1.81
t-Bu	0.35

^a Data from Yakimovich *et al.* (86ZOR286); determined by ¹H-NMR in CDCl₃ solution at 30°C.

The *N*-benzoylhydrazones of methyl 4-aryl-2,4-dioxobutanoates **76** ($R^1 = \text{XC}_6\text{H}_4$; $R^2 = \text{Ph}$) (81ZOR284) have been isolated as several isomers in the solid state (see Table XIII), depending on the substituent X. In CDCl₃ solution, the equilibrium **76A-Z** \rightleftharpoons **76A-E** \rightleftharpoons **76B** (Table XIII) appears, with predominance of the open-chain tautomer **76A-Z**, stabilized by an intramolecular hydrogen bond. In (CD₃)₂SO solution, the equilibrium shifts toward the pyrazoline tautomer **76B**. Among the open-chain tauto-

TABLE XIII
EQUILIBRIUM CONSTANTS^a FOR METHYL 4-ARYL-2,4-DIOXOBUTANOATE
N-BENZOYLHYDRAZONES **76** ($R^1 = \text{XC}_6\text{H}_4$; $R^2 = \text{Ph}$)^b

X	Structure in solid state	In CDCl ₃			In (CD ₃) ₂ SO		
		K_T	$(K_T)_1$	$(K_T)_2$	K_T	$(K_T)_1$	$(K_T)_2$
4-Me ₂ N	A - Z	0	0	0	0.16	1.00	0.19
4-MeO	A + B	0.39	0.53	1.47	0.89	11.75	0.90
4-Me	A + B	0.61	0.72	4.22	1.86	21.67	2.03
H	A + B	0.92	1.07	6.86	3.17	25.33	3.62
4-Cl	B	2.03	2.31	16.75	6.89	>99	6.89
3-NO ₂	B	19.0	19.0	99	24.0	>99	24.0
4-NO ₂	B	>99	>99	>99	>99	>99	99

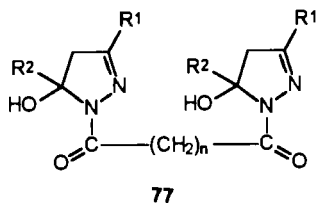
^a $K_T = [\mathbf{B}]/[\mathbf{A} - Z + \mathbf{A} - E]$; $(K_T)_1 = [\mathbf{B}]/[\mathbf{A} - Z]$; $(K_T)_2 = [\mathbf{B}]/[\mathbf{A} - E]$. ^b Data from Yakimovich and Nikolaev (81ZOR284), determined by ¹H-NMR at 30°C.

mers, the hydrazone **76A-E** predominates, due to destruction of the intramolecular hydrogen bond in **76A-Z** by the proton-accepting solvent.

Good correlations between the equilibrium constants K_T , $(K_T)_1$, and $(K_T)_2$ (see Table XIII) and the constants σ of substituents X have been obtained:

$$\begin{aligned}\log K_T &= -0.02 + 1.7\sigma; & n &= 5; & r &= 0.994; & s_0 &= 0.004; \\ \log (K_T)_1 &= 0.09 + 1.58\sigma; & n &= 5; & r &= 0.993; & s_0 &= 0.005; \\ \log (K_T)_2 &= 0.81 + 1.96\sigma; & n &= 4; & r &= 0.968; & s_0 &= 0.009.\end{aligned}$$

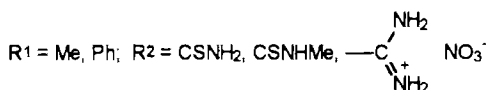
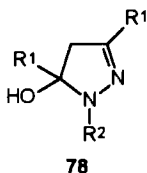
On the interaction of 1,3-diketones with dihydrazides of oxalic and malonic acids, the condensation products have been obtained in a molar ratio of 2:1 (88ZOR1823). In the solid state, they exist as the bispyrazolines **77**; but in solution, equilibria are observed. These equilibria occur with the participation of the bispyrazoline tautomer, involving two diastereomers, and also of tautomers containing hydrazone and/or enhydrazine fragments.



The systematic investigations on the structure and tautomerism of 1,3-dicarbonyl compound *N*-acylhydrazones by Yakimovich and co-workers (84MI1; 88MI6, 88TH2) allowed them to report on a number of papers [76JHC257; 77JHC367; 78JHC385; 82IJC(A)1137; 83IJC(B)496, 83IJC(B)499, 83RRC981] in which a hydrazone, or even an hydrazinoenol, structure was erroneously attributed to the corresponding 5-hydroxypyrazolines.

The condensation products (1:1) of pentane-2,4-dione and 1,3-diphenylpropane-1,3-dione with thiosemicarbazide, 4-methylthiosemicarbazide, and aminoguanidinium nitrate were formed (86KGS128; 87ZOB584; 90-KGS1260) as the cyclic isomers **78**, which sometimes readily underwent dehydration to the corresponding pyrazoles.

Ring-chain equilibria involving cyclic tautomer formation by intramolecular reversible amidrazone NH-group addition to the C=O bond were observed (85KGS849; 86ZOR500) in solutions of the products formed in the reactions of pentane-2,4-dione and its 3-methyl derivatives with benzamidrazinium iodides. The ring-chain equilibrium was detected only in solutions of iodides or picrates. The free bases exist as the open-chain tautomers, like the hydrazones or enhydrazines. In contrast with the acyl-



hydrazones of pentane-2,4-dione **75** ($R^1 = R^3 = \text{Me}$), for which a considerable stabilization of the cyclic tautomer **75B** was observed after the introduction of a methyl group at position 3 (**75**, $R^2 = \text{Me}$), the series of benzamidrazonium ions **79** ($R^3 = \text{Ph}$) exhibits an opposite effect (see Table XIV). In contradiction with the Thorpe–Ingold effect (I-257), the introduction of one or two methyl groups at the carbon atom in the chain between interacting centers unexpectedly led to a considerable shift in the equilibrium **79A** \rightleftharpoons **79B** ($R^1 = \text{H}$; $R^2 = \text{Me}$; or $R^1 = R^2 = \text{Me}$) in favor of the open-chain tautomer. It is likely that the sterically very rigid amidrazonium group has steric demands for the ring closure that do not favor α -substitution. Moreover, the isomerization **79A-Z** \rightarrow **79A-E**, which must precede the ring closure, is forbidden for the dimethyl-substituted derivative **79A** ($R^1 = R^2 = \text{Me}$) because the intermediate **79A'** in such a transformation cannot be formed. On passing from the benzamidrazonium **79** ($R^3 = \text{Ph}$) to the acetamidrazonium ($R^3 = \text{Me}$) ion, the entire equilibrium shifts in favor of the cyclic tautomer. After the introduction of a methyl group at

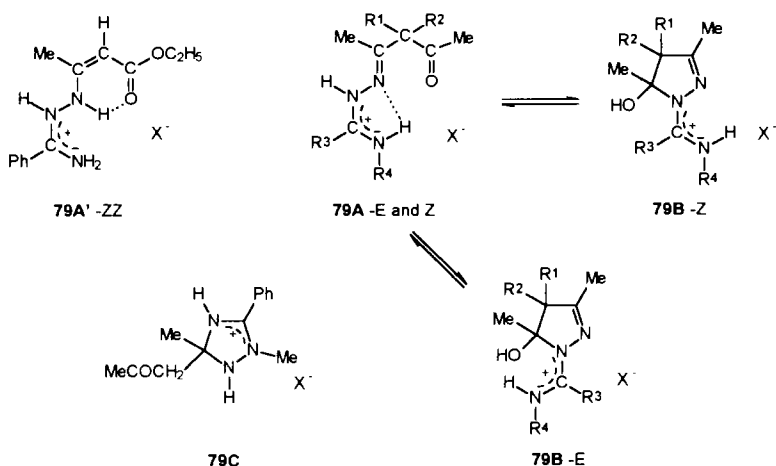


TABLE XIV
 RING-CHAIN EQUILIBRIUM **79A** \rightleftharpoons **79B** CONSTANTS^a

R ¹	R ²	R ³	R ⁴	X	Content (%)			$K_T = [\mathbf{B-E} + \mathbf{B-Z}]/[\mathbf{A-E, Z}]$
					A-E and Z	B-Z	B-E	
H	H	Ph	H	I	9	61	30	10.1
H	Me	Ph	H	I	40	48	12	1.5
Me	Me	Ph	H	I	100			0
H	H	Ph	Me	picrate	9	80	11	10.1
H	H	Me	H	I	0	65	35	>99

^a Data from Khurstaler *et al.* (86ZOR500); determined by ¹H-NMR in (CD₃)₂SO.

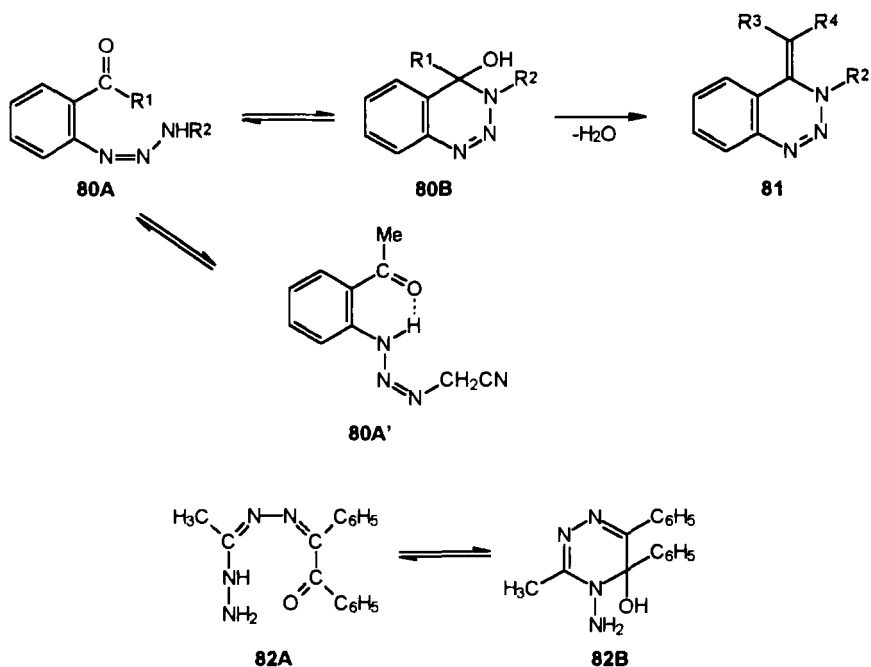
N(2) of benzamidrazinium, the only product in the reaction with pentane-2,4-dione was 1,2,4-triazolinium iodide **79C**. This isomer is formed by intramolecular NH-group addition to the C=N bond. The formation of a seven-membered 1,2,4-triazepine isomer has not been detected.

7. Hydroxytriazine Derivatives

The ring-chain equilibrium **80A** \rightleftharpoons **80B** has been observed (83CJC179; 85CJC2455; 86CJC250; 87CJC292) in solutions of 4-hydroxy-3,4-dihydro-1,2,3-benzotriazines. The tautomerization is accompanied by the ready dehydration **80B** \rightarrow **81**, especially in the derivatives **80** (R¹ = Me; R² = alkyl) (75CJC3714).

A decrease in the nitrogen atom nucleophilicity by introduction of an aryl group stabilizes the open-chain isomers **80A** (R¹ = Me; R² = 4-XC₆H₄, X = H; MeO, MeCO, MeOOC) (75CJC3714). Stable cyclic isomers were isolated for the derivatives **80** (R¹ = H; R² = Me, Et, PhCH₂, Ph; or R¹ = Ar; R² = Me), which are incapable of dehydration for structural reasons (R¹ = H or Ph) (83CJC179).

The triazines **80B** (R¹ = Me; R² = Me, PhCH₂) were isolated [84 ACS(B)185] in the solid state as cyclic isomers. They retain this structure in (CD₃)₂SO solution, but in CDCl₃ the equilibrium **80A** \rightleftharpoons **80B** ($K_T \sim 1$, ¹H-NMR) was detected for the triazine **80B** (R¹ = R² = Me). Simultaneously, a slow dehydration takes place in CDCl₃. The duration of complete dehydration varies from 1 day to 1 week, depending on the amounts of impurities. The equilibrium was fully shifted toward the open-chain tautomer in a CDCl₃ solution of triazine **80B** (R¹ = Me; R² = PhCH₂). By means of ¹³C-NMR spectroscopy, the equilibrium **80A** \rightleftharpoons **80B** was detected in CDCl₃ solutions of the derivatives **80B** (R¹ = H, Ph; R² = ClCH₂CH₂), which exist in the solid state as cyclic isomers (87CJC292). The complete



shift of the equilibrium toward the open-chain tautomer was detected in CDCl_3 solutions of the triazines **80B** ($\text{R}^1 = \text{Et}$; $\text{R}^2 = \text{ClCH}_2\text{CH}_2$; and $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{NCCH}_2$), but the ^{13}C -NMR data indicate that the open-chain tautomers of **80** ($\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{NCCH}_2$; and $\text{R}^1 = \text{R}^2 = \text{Me}$) are stabilized by an intramolecular hydrogen bond (**80A'**) formed after $\text{N}=\text{N}$ double-bond migration in the open-chain tautomer **80A** (85CJC2455).

4-Amino-4,5-dihydro-5-hydroxy-1,2,4-triazine (**82B**) exhibits a temperature-dependent equilibrium with the open-chain hydrazide-hydrazone derivative **82A** in CDCl_3 solution, as shown by the ^1H -NMR data (85LA78).

D. ADDITION OF A SH GROUP

Ring-chain tautomerism of this type has been investigated relatively rarely. It is generally known that sulfur is more nucleophilic than oxygen. Thus, if the structure of the connecting link does not hinder the intramolecular addition, cyclic isomers predominate. They are often subject to further dehydration reactions or to more complicated transformations. Since the SH group is more acidic than the OH group, the corresponding anions usually possess the open-chain structure.

It has been shown by thermodynamic calculations (89TH1) that, under equal structural conditions, the ratio of the tautomeric equilibrium constants for the reversible addition reaction of the SH group and that for the OH group should be $\sim 10^5$ in favor of the sulfur addition product. A similar result ($>10^4$) was estimated (90T6545) from a comparison of the stability of the 1,3-thiazolidine ring with that of the 1,3-oxazolidine ring.

6-Hydroxy-6-methyltetrahydro-1,3-thiazine-2-thiones **83B** ($R^1 = \text{Me}$; $R^2 = \text{H}$; or $R^1 = \text{H}$; $R^2 = \text{Me}$; or $R^1 = R^2 = \text{Me}$) exist in the solid state as cyclic isomers, but exhibit a slowly reached (6–18 hours) equilibrium **83A** \rightleftharpoons **83B** in chloroform solution. By means of IR spectroscopy, it was shown that the introduction of a methyl group at position 5 ($R^1 = \text{Me}$) destabilizes the cyclic tautomer **83B**, while two methyl groups at position 4 ($R^2 = \text{Me}$) act strongly in the opposite direction. Mass spectroscopy has revealed that in the gas phase these compounds exist almost entirely as open-chain tautomers (92KGS985).



E. INTRAMOLECULAR ACYL GROUP MIGRATION

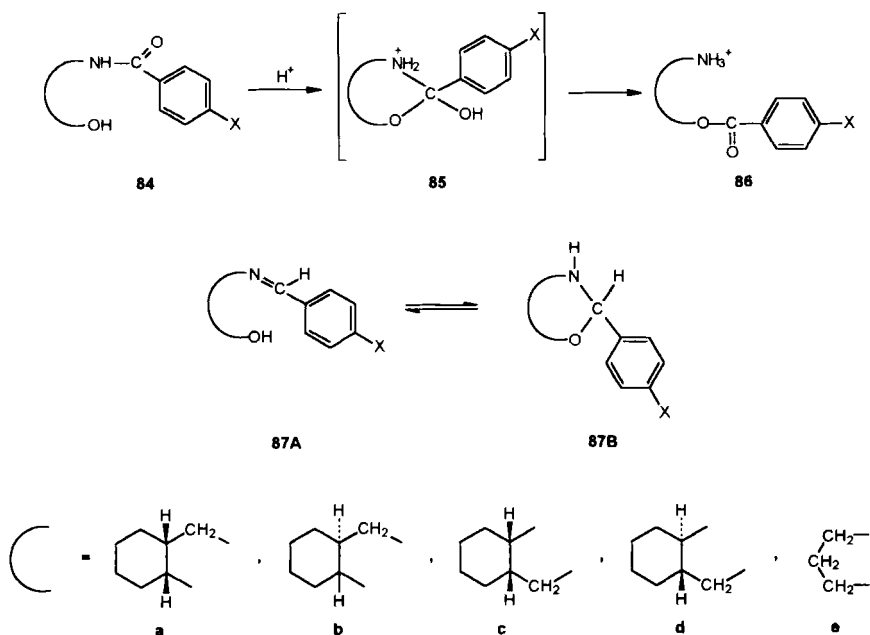
The intramolecular migration of acyl functions is related to chemical transformations that occur via the scheme chain-[ring]-chain. The close relationship of these reactions with the ring-chain tautomerism under consideration is best demonstrated by the fact that both of these transformations proceed by intramolecular nucleophilic addition to the C=O bond. The process of intramolecular acyl-group migration generally takes places via the tetrahedral cyclic intermediate of low stability [81ACR306; 85APO(21)37; 87MI2; 89ZSK141].

An interesting example presented by Fülöp *et al.* (87JOC3821) confirms that the structural factors governing the intramolecular addition of XH groups to the C=Y bonds in ring-chain tautomeric systems control intramolecular acyl migrations in the same way. A good linear correlation was obtained (87JOC3821) between the rate constants for the intramolecular N \rightarrow O migration reactions of the aroyl group in *N*-aroylalcohols **84a-d** \rightarrow **86** ($X = \text{H, Me, NO}_2$) [68TL2713, 68TL4441; 70ACH(65)347] and the c values calculated for the ring-chain equilibrium system **87A** \rightleftharpoons **87B** containing the same connecting-link structures (**a-e**):

$$c = \log(K_T)_0^Y - \log(K_T)_0^{\text{ref}},$$

where $(K_T)_0^Y$ is the ring-chain equilibrium constant of the system $\mathbf{87A} \rightleftharpoons \mathbf{87B}$ ($X = H$) and Y is one of the connecting link structures **a-d**; $(K_T)_0^{\text{ref}}$ is the corresponding constant for $\mathbf{87e}$, which has an unsubstituted trimethylene connecting link and is used here as the reference system.

The above correlation provides indirect proof that the rate-limiting step in the acyl-group migration $\mathbf{84} \rightarrow \mathbf{86}$ is the formation of the intermediate $\mathbf{85}$ [87JOC3821; 94ACH(131)697].



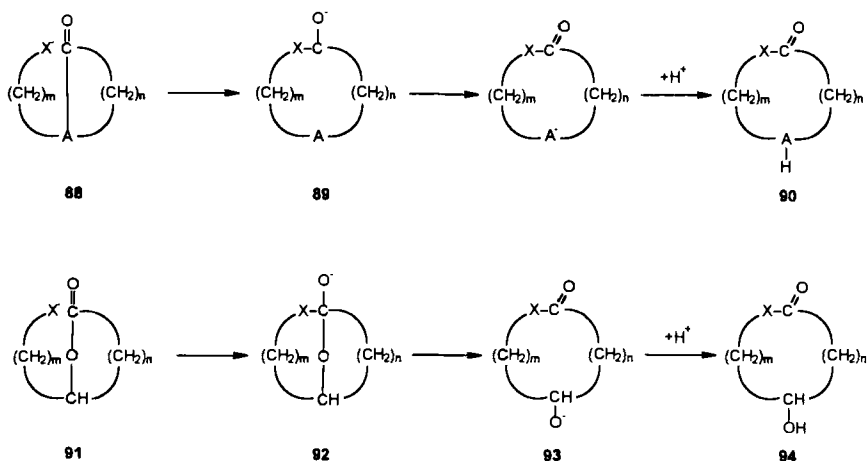
The value of c characterizes the contribution of the connecting-link structure (in this case represented by **a-d**) in the stabilization ($c > 0$) or destabilization ($c < 0$) of the corresponding cyclic tautomeric form, in comparison with the system (in this case **e**) chosen as reference [94ACH(131)697] (for a more detailed discussion, see Part II).

F. CYCLOLS

The formation of macrocycles through ring-enlargement reactions via bicyclic tetrahedral intermediates—i.e., the cyclols of general type **89** or **92** (the ionized forms are shown), which are mostly unstable and can be

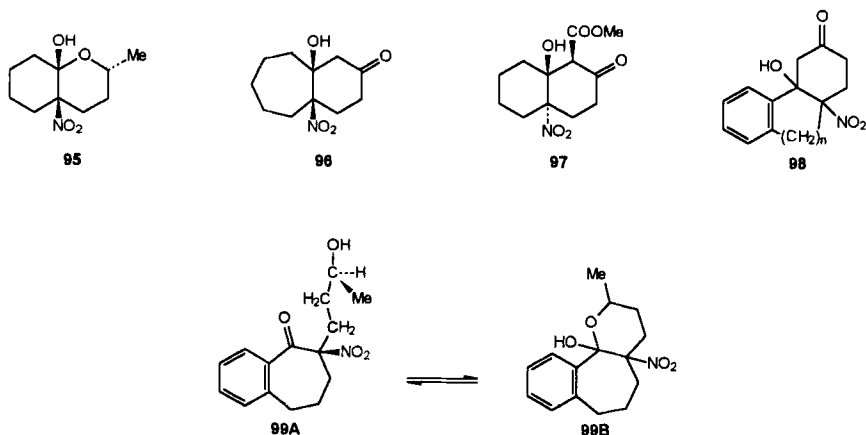
detected or isolated only rarely (88T1573; 91MI1)—is a particular case of intramolecular acyl-group migration (intramolecular transacylation).

In the scheme $88 \rightarrow 90$, $X = O, NH$, or CR_2 , and $A = N$ or $C-Y$, where $Y = COR, SO_2R, NO_2, CH_2N^+R_3, NO$, or $COOR$. In the transactonization reactions $91 \rightarrow 94$, $X = O$ (77JA7359).



Some of these reactions led to isolation of the intermediate cyclols **95** (82HCA249; 84HCA1713), **96** and **97** (83HCA845), and **98** ($n = 2, 3$) (87HCA2166).

A ring-chain equilibrium $99A \rightleftharpoons 99B$ was detected (87HCA2166), which was attained in C_6D_6 solution 14 days after dissolution ($K_T = 1.5$, 1H -NMR).



All the cyclols isolated were isomerized into the corresponding macrocycles on basic catalysis.

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***S*-, *Se*-, and *Te*- (Perfluoroalkyl)dibenzothiophenium, -selenophenium, and -tellurophenium Salts**

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I. Introduction	323
II. Synthesis	324
A. Synthesis of <i>S</i> - and <i>Se</i> -(Perfluoroalkyl)dibenzothiophenium and -selenophenium Salts and Their Analogs	324
B. Synthesis of <i>Te</i> -(Perfluoroalkyl)dibenzotellurophenium Salts	326
C. Nitration of <i>S</i> -, <i>Se</i> -, and <i>Te</i> -(Perfluoroalkyl)dibenzothiophenium, -selenophenium, and -tellurophenium Salts	327
D. Sulfonation of <i>S</i> -, <i>Se</i> -, and <i>Te</i> -(Perfluoroalkyl)dibenzothiophenium, -selenophenium, and -tellurophenium Salts	328
III. Properties	328
IV. ¹⁹ F Nuclear Magnetic Resonance	329
V. Perfluoroalkylation	329
A. Trifluoromethylation	329
1. Trifluoromethylation of Carbanions	331
2. Trifluoromethylation of Enol Trimethylsilyl Ethers	332
3. Trifluoromethylation of Enamines	332
4. Trifluoromethylation of Aromatics	332
5. Trifluoromethylation of Thiolate Anions	333
6. Trifluoromethylation of Halide Anions	334
7. Trifluoromethylation of Phosphines	334
8. Trifluoromethylation of Enolate Anions with a Suitable Combination of Boron Lewis Acids	334
B. Perfluorobutylation and -octylation	337
VI. Kinetics of Trifluoromethylation	337
References	338

I. Introduction

A number of *S*-, *Se*-, and *Te*-alkylated heterocyclic onium salts have been synthesized and their properties and reactivities reported [74JA7835; 84MI1; 90HOU(E12b)676]. Until now, however, the corresponding per-

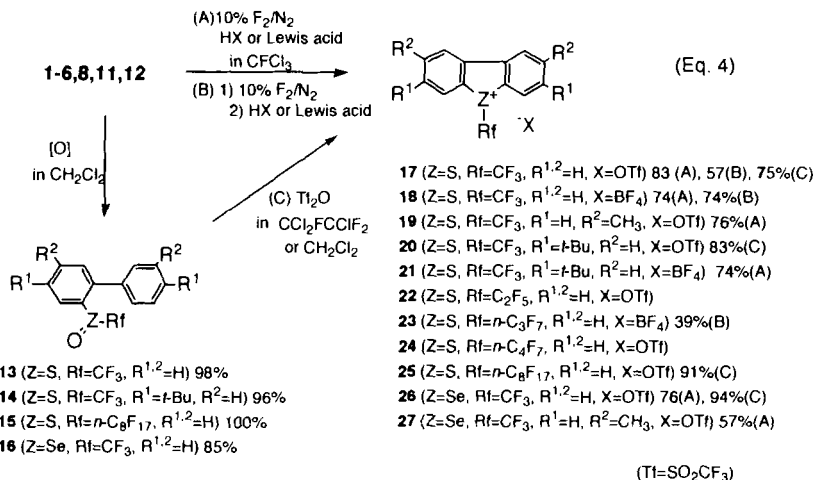
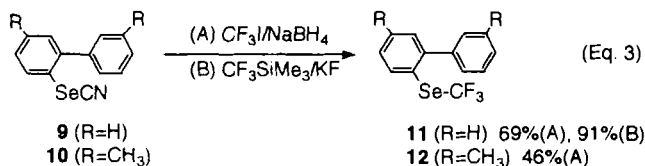
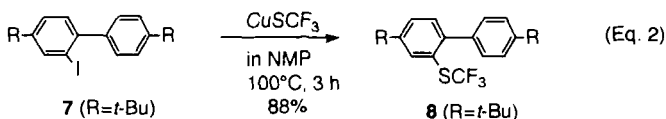
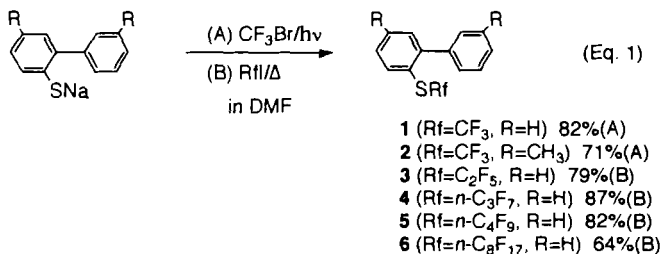
fluoroalkylated heterocyclic onium salts had not been reported. A perfluoroalkyl group is a strongly electron-withdrawing group, quite different from an alkyl group which is a relatively strong electron-donating group. The electronegativity of a trifluoromethyl group (CF_3) is 3.45, while that of a methyl group is 2.28 (65JPC3284). On the other hand, developing useful electrophilic perfluoroalkylating agents is an important subject, since introduction of a perfluoroalkyl group to a material brings about a change in its chemical, physical, or biochemical properties (69MI1; 73MI1; 82MI1; 93MI1; 94MI1). Although (perfluoroalkyl)phenyliodonium triflates (FITS reagents) (83YGK251; 84BCJ3361; 86BCJ439, 86JFC37) were developed as widely applicable electrophilic perfluoroalkylating agents containing two or more carbons, an effective electrophilic trifluoromethylating agent was not developed. Yagupol'skii and his co-workers reported *S*-(trifluoromethyl)(*p*-chlorophenyl)(2,4-dimethylphenyl and *p*-methoxyphenyl)sulfonium hexafluoroantimonates as trifluoromethylating agents, which were prepared by treatment of *p*- $\text{ClC}_6\text{H}_4\text{SOCF}_3$ with $\text{SF}_3^+ \text{SbF}_6^-$ followed by condensation with *m*-xylene and anisole, respectively (84JOU103). However, the sulfonium salts do not react with *N,N*-dimethylaniline, a strongly activated aromatic, even at elevated temperature, although they react with sodium *p*-nitrobenzenethiolate to give *p*-(trifluoromethylthio)nitrobenzene. Thus, *S*-, *Se*-, and *Te*-perfluoroalkylated dibenzoheterocyclic onium salts were expected to have interesting and useful properties and reactivities as new reagents.

II. Synthesis

A. SYNTHESIS OF *S*- AND *Se*- (PERFLUOROALKYL)DIBENZOTHIOPHENIUM AND -SELENOPHENIUM SALTS AND THEIR ANALOGS (93JA2156)

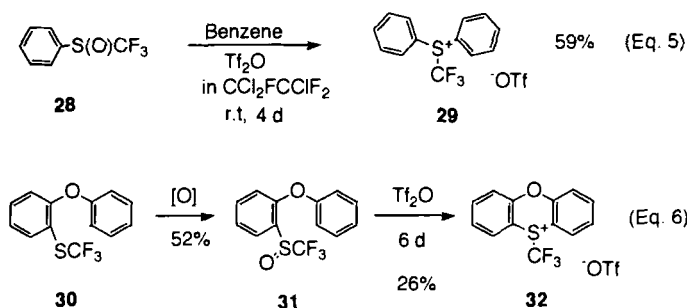
Trifluoromethyl biphenyl sulfides **1** and **2** were prepared by irradiating a mixture of the corresponding sodium 2-biphenylthiolates and trifluoromethyl bromide in dimethylformamide (DMF) at 0°C with a high-pressure Hg lamp (Eq. 1). Perfluoroalkyl biphenyl sulfides **3–6** were prepared by the reaction of the sodium biphenylthiolates with perfluoroalkyl iodide at room temperature. Sulfide **8** was prepared by the reaction of iodide **7** with [(trifluoromethyl)thio]copper(I) (Eq. 2). Trifluoromethyl biphenyl selenides **11** and **12** were prepared by treating selenocyanatobiphenyls **9** and **10** with sodium borohydride in the presence of trifluoromethyl iodide at –30°C to room temperature (Eq. 3). However, this method required a large excess of trifluoromethyl iodide to get selenides **11** and **12** in good

yields. Treating selenocyanatobiphenyl **9** with (trifluoromethyl)trimethylsilane in dimethyl sulfoxide (DMSO) at room temperature for 0.5 h in the presence of a catalytic amount of KF gave **11** in high yield (Eq. 3) (93UP1).



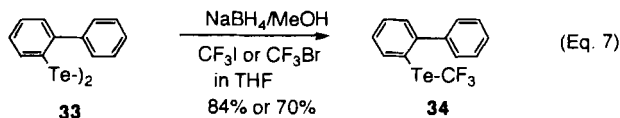
The *S*- and *Se*-(perfluoroalkyl)dibenzothiophenium salts **17–27** were synthesized according to three methods (Eq. 4): (1) fluorination of the corresponding sulfide **1–6** or **8** or selenide **11** or **12** with F_2 in the presence of an acid or a Lewis acid; (2) fluorination with F_2 , followed by treatment with an acid or a Lewis acid; and (3) treatment of sulfoxide **13**, **14**, or **15** or selenoxide **16** with triflic anhydride (Tf_2O). Sulfoxides **13–15** and selenoxide **16** were prepared by oxidation of the corresponding sulfides or selenide with *m*-chloroperbenzoic acid.

S-(Trifluoromethyl)diphenylsulfonium triflate (**29**) and *S*-(trifluoromethyl)phenoxathiinium triflate (**32**) were synthesized as shown in Eqs. 5 and 6.



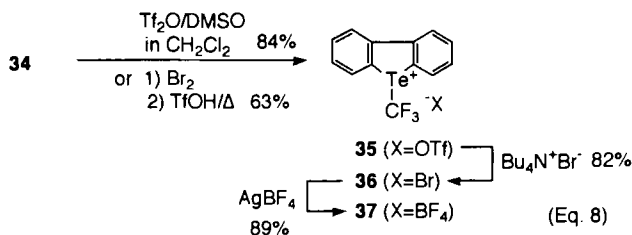
B. SYNTHESIS OF *Te*-(PERFLUOROALKYL)DIBENZOTELLUROPHENIUM SALTS (93JA2156)

Biphenyl ditelluride **33** was treated with sodium borohydride/methanol in the presence of trifluoromethyl iodide or bromide in tetrahydrofuran (THF) to give trifluoromethyl biphenyl telluride **34** (Eq. 7).



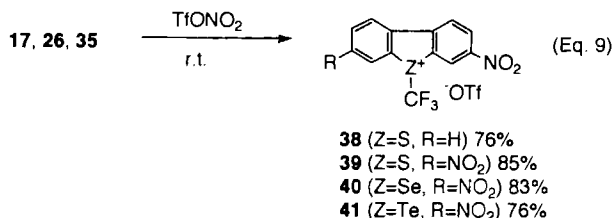
Telluride **34** was treated with triflic anhydride in the presence of 1 equivalent of DMSO in dichloromethane at room temperature to give *Te*-(trifluoromethyl)dibenzotellurophenium triflate (**35**). Triflate **35** was also synthesized by treating **34** with bromine in 1,1,2-trichloroethane at room temperature followed by triflic acid at reflux temperature. Triflate **35** was converted to bromide **36** by treatment with tetrabutylammonium bromide

in acetonitrile at room temperature. Treatment of **36** with silver tetrafluoroborate in acetonitrile at reflux temperature gave tetrafluoroborate **37** (Eq. 8).

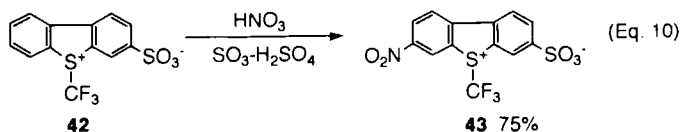


C. NITRATION OF *S*-, *Se*-, AND *Te*- (PERFLUOROALKYL)DIBENZOTHIOPHENIUM, -SELENOPHENIUM, AND -TELLUROPHENIUM SALTS (93JA2156)

S-Triflate was treated with about 1.3 equivalents of nitronium triflate in nitromethane at room temperature overnight to give mononitro triflate **38**. The nitronium salt was prepared *in situ* by mixing 94% concentrated nitric acid and triflic anhydride at room temperature. Treating **17** with about 3 equivalents of nitronium triflate without using nitromethane solvent gave dinitro triflate **39**. *Se*-Triflates (**26**) and *Te*-triflates (**35**) were similarly dinitrated to give triflates **40** and **41**, respectively (Eq. 9).

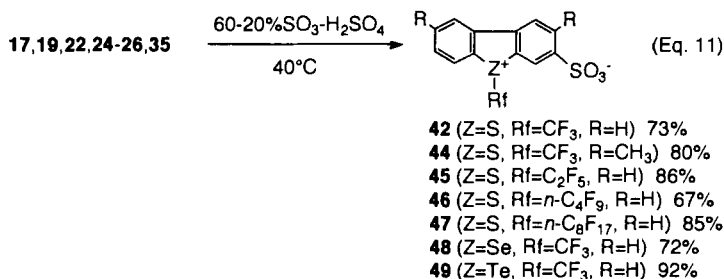


S-Sulfonate **42** was nitrated with a mixture of concentrated nitric and fuming sulfuric acids to give nitro *S*-sulfonate **43** (Eq. 10) (95JFC).



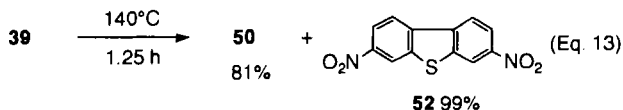
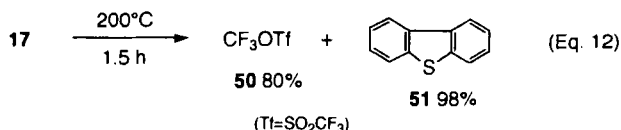
**D. SULFONATION OF *S*-, *Se*-, AND *Te*-
(PERFLUOROALKYL)DIBENZOTHIOPHENIUM, -SELENOPHENIUM, AND
-TELLUROPHENIUM SALTS (95JFC)**

S-Triflate **17** was treated with 60% fuming sulfuric acid to give *S*-sulfonate **42**. Similarly, *S*-sulfonates **44–47**, *Se*-sulfonate **48**, and *Te*-sulfonate **49** were synthesized (Eq. 11).



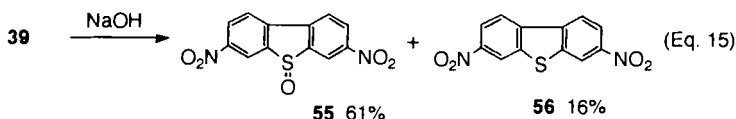
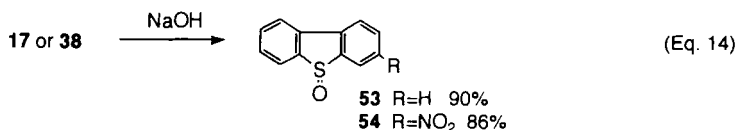
III. Properties (93JA2156)

All the *S*-, *Se*-, and *Te*-(perfluoroalkyl)dibenzothiophenium, -selenophenium, and -tellurophenium salts synthesized above are stable crystalline materials at room temperature. Their melting or decomposition points (dec. p) are higher than 100°C. Nitro substituents decrease their stability [*S*-salt **17** mp 155°C > dinitro *S*-salt **39** dec. p 130–135°C]. The chalcogen stability increases in the order S < Se < Te [dec. p: *S*-salt **39** 130–135°C < *Se*-salt **40** 198–200°C < *Te*-salt **41** 275–280°C]. Thermolysis of *S*-salt **17** at 200°C gave trifluoromethyl triflate (**50**) and dibenzothiophene (**51**) in high yields (Eq. 12). Thermolysis of dinitro *S*-salt **39** at 140°C gave **50** and dinitrodibenzothiophene **52** (Eq. 13).

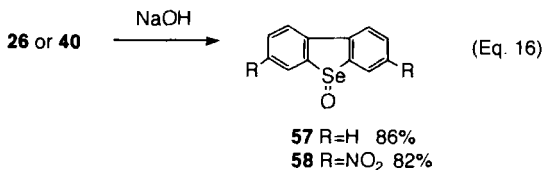


Alkaline hydrolysis of *S*-salt **17** and mononitro *S*-salt **38** gave dibenzothiophene *S*-oxides **53** and **54**, respectively (Eq. 14). But, dinitro *S*-salt **39** gave

a mixture of dinitrodibenzothiophene *S*-oxide **55** and a reduction product, dinitrodibenzothiophene **56** (Eq. 15).



Both *Se*-salt **26** and dinitro *Se*-salt **40** gave dibenzoselenophene *Se*-oxide **57** and its dinitro derivative **58**, respectively (Eq. 16).



IV. ^{19}F Nuclear Magnetic Resonance (93JA2156)

The ^{19}F CF_3 chemical shifts of each of the *S*- and *Se*-(trifluoromethyl)dibenzothiophenium and -selenophenium triflates were linearly correlated with Hammett's substituent constants σ_p or σ_m , as evident from Fig. 1. This indicated that the electron density of the trifluoromethyl group is linearly correlated with the electronic nature of the substituents attached to the dibenzoheterocyclic salts. These ^{19}F CF_3 chemical shifts are in good agreement with the order of trifluoromethylating power, as discussed below.

V. Perfluoroalkylation

A. TRIFLUOROMETHYLATION (93JA2156)

The trifluoromethylating order of reactivity of a series of *S*-, *Se*-, and *Te*-(trifluoromethyl)dibenzothiophenium, -selenophenium, and -tellurophenium triflates was determined by relative reaction rates with aniline.

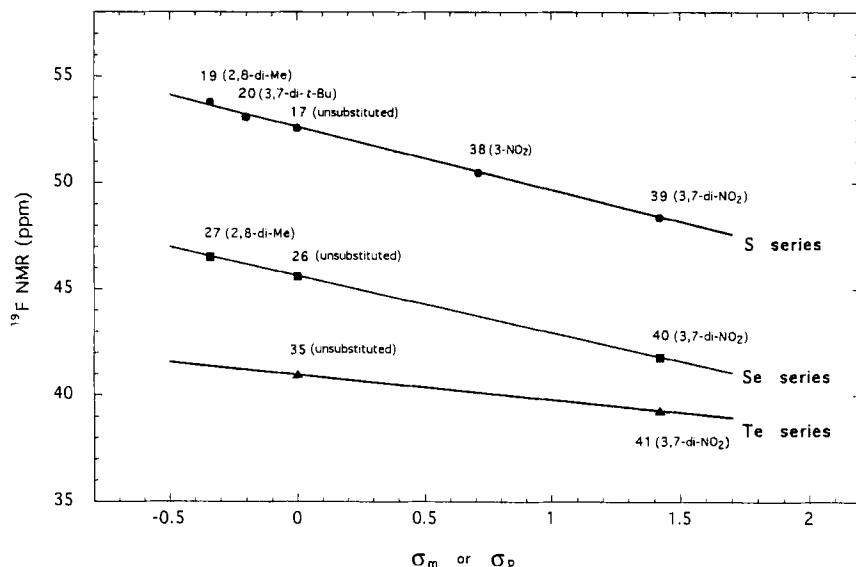
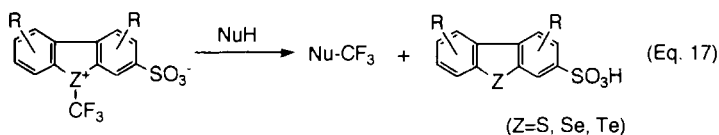


FIG. 1. Relationship between ^{19}F CF_3 chemical shifts of *S*-, *Se*-, and *Te*-(trifluoromethyl)-dibenzothiophenium, -selenophenium, and -tellurophenium triflates and Hammett's constants σ_m or σ_p for the ring substituents; *S*, *Se*, and *Te* refer to substituted and unsubstituted *S*-, *Se*-, and *Te*-(trifluoromethyl)dibenzothiophenium, -selenophenium, and -tellurophenium triflates, respectively. The numbers on the lines are the compound numbers shown in the text. Substituents and their substitution positions are shown in the parentheses. The smaller the ^{19}F NMR chemical shift is, the more downfield is the resonance (CFCl_3 served as an internal standard in CD_3CN).

Thus, reactivity increases in the order $\text{Te} < \text{Se} < \text{S}$ atom and 2,8-dialkyl $<$ 3,7-dialkyl $<$ H $<$ 3- NO_2 $<$ 3,7-di- NO_2 . For mixed heterocyclic salts, the order differed, apparently being determined by the electron deficiency of the CF_3 group due to the electron-withdrawing or -donating effects of chalcogens and ring substituents, rather than the inherent nature of the chalcogens. The determined order was as follows; *Te*-salt **35** $<$ 2,8-dimethyl *S*-salt **19** $<$ 3,7-di-*t*-butyl *S*-salt **20** $<$ *Se*-salt **26** \leq dinitro *Te*-salt **41** $<$ *S*-salt **17** $<$ mononitro *S*-salt **38** $<$ dinitro *Se*-salt **40** $<$ dinitro *S*-salt **39**. Nuncyclic *S*-salt **29** is much less reactive than dibenzoheterocyclic *S*-salt **17** and the power of **29** is situated between those of *Te*-salt **35** and 2,8-dimethyl *S*-salt **19**. This variation made possible the trifluoromethylation of a wide range of nucleophilic substrates differing in reactivity. In general, reactive substrates were well trifluoromethylated by less powerful trifluoromethylating agents such as *Se*-salt **26** and dimethyl *S*-salt **19**, while less reactive substrates were well trifluoromethylated by more powerful reagents such as dinitro *S*-salt **39**. Intermediately reactive substrates were well trifluoro-

methyated by moderately powerful reagents such as *S*-salt **17**. Thus, a new field, electrophilic trifluoromethylation, has been established by using this "power-variable" dibenzoheterocyclic salt system. The products obtained by this electrophilic trifluoromethylation are otherwise impossible or difficult to obtain by conventional nucleophilic or free-radical trifluoromethylation (90TA661; 91T3207, 91YGK612; 92T6555).

Counteranion-bound *S*-, *Se*-, and *Te*-(trifluoromethyl)dibenzothiophenium-, -selenophenium-, and -tellurophenium-3-sulfonates **42–44**, **48**, and **49**, developed as another series of the electrophilic trifluoromethylating agents, are useful because the resultant trifluoromethylated products are easily separated from the by-product dibenzothiophene-, -selenophene-, or -tellurophene-3-sulfonic acids because these by-products are soluble in water (Eq. 17) (95JFC).

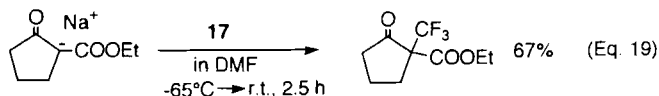
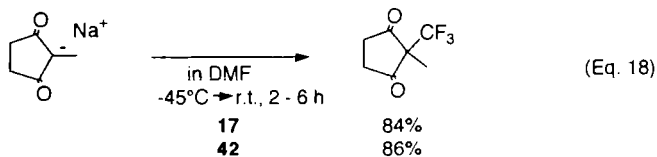


In contrast, non-counteranion-bound salts **17–27** and **38–41** produced as by-products dibenzothiophene, -selenophene, -tellurophene, or their derivatives, which are insoluble in water.

The relative reactivity of the counteranion-bound salts is expected to increase in the order *Te*-sulfonate **49** < dimethyl *S*-sulfonate **44** < *Se*-sulfonate **48** < *S*-sulfonate **42** < nitro *S*-sulfonate **43**. The reactivity of *S*-sulfonate **42** is the same as that of non-counteranion-bound *S*-triflate **17** (95JFC).

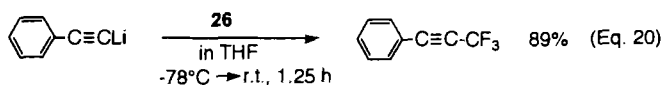
1. Trifluoromethylation of Carbanions

Sodium salts of β -diketones or β -keto esters were trifluoromethylated with *S*-triflate **17** or *S*-sulfonate **42** in good yields (Eqs. 18, 19). The sodium



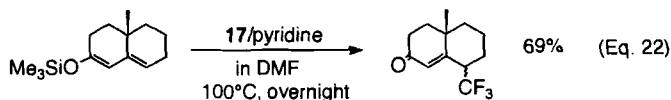
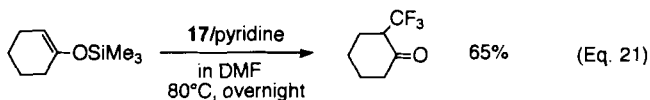
salt of diethyl 2-methylmalonate was trifluoromethylated with **17** to give diethyl 2-methyl-2-(trifluoromethyl)malonate in 38% yield.

Lithium phenylacetylide was trifluoromethylated with the less powerful *Se*-triflate **26** in high yield (Eq. 20).



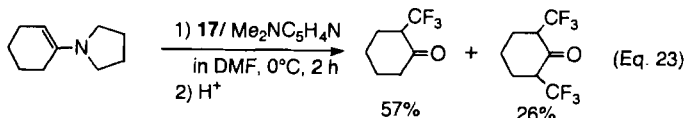
2. Trifluoromethylation of Enol Trimethylsilyl Ethers

Enol trimethylsilyl ethers were trifluoromethylated with *S*-salt **17** in the presence of an equimolar amount of pyridine to give trifluoromethyl ketones in good yields (Eqs. 21, 22).



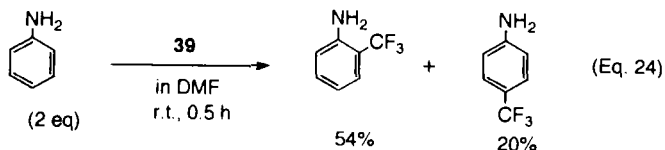
3. Trifluoromethylation of Enamines

An enamine was trifluoromethylated with *S*-salt **17** (1 equivalent) in the presence of an equimolar amount of 4-(dimethylamino)pyridine to give mono(trifluoromethyl) and di(trifluoromethyl) ketones (Eq. 23).

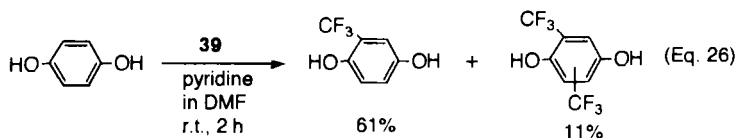
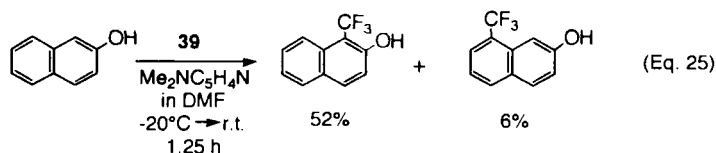


4. Trifluoromethylation of Aromatics

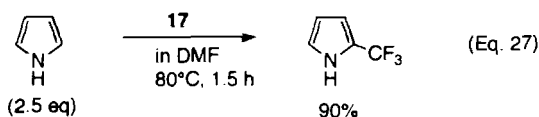
Aniline was smoothly trifluoromethylated with the most powerful dinitro *S*-salt **39** to give a mixture of *o*- and *p*-CF₃ isomers (Eq. 24).



Naphthol and *p*-hydroquinone were smoothly trifluoromethylated with **39** in the presence of 4-(dimethylamino)pyridine or pyridine (Eqs. 25, 26) as an acid trap.

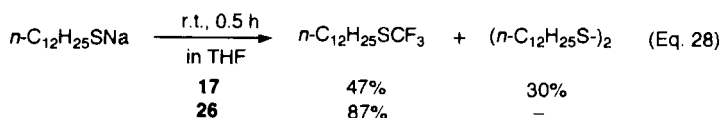


Pyrrole was trifluoromethylated with *S*-salt **17** at an elevated temperature (Eq. 27).

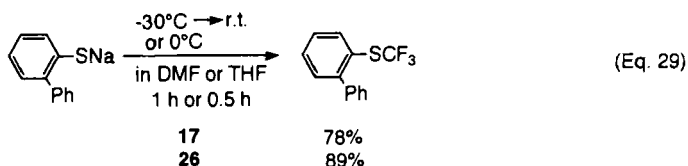


5. Trifluoromethylation of Thiolate Anions

Sodium alkanethiolate was treated with *S*-salt **17** to give a disulfide in addition to a trifluoromethyl alkyl sulfide (Eq. 28). However, less powerful

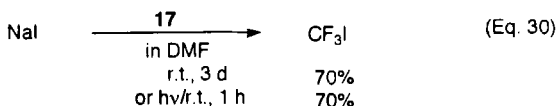


Se-salt **26** afforded a high yield of the trifluoromethyl alkyl sulfide. With sodium arenethiolate, both *S*-salt **17** and *Se*-salt **26** gave high yields of trifluoromethyl aryl sulfide (Eq. 29).



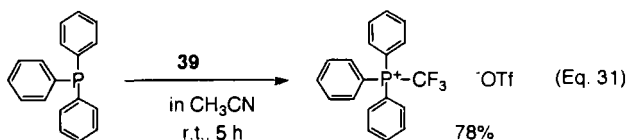
6. Trifluoromethylation of Halide Anions

Treatment of *S*-salt **17** with sodium iodide gave trifluoromethyl iodide (Eq. 30). Irradiation with a high-pressure Hg lamp readily produced trifluoromethyl iodide in the same yield.



7. Trifluoromethylation of Phosphines

Treatment of the most powerful dinitro *S*-salt **39** with triphenylphosphine gave (trifluoromethyl)triphenylphosphonium triflate in good yield (Eq. 31). However, moderately powerful *S*-salt **17** did not produce the phosphonium triflate even at an elevated temperature.



8. Trifluoromethylation of Enolate Anions with a Suitable Combination of Boron Lewis Acids (94JOC5692)

None of the trifluoromethyl dibenzoheterocyclic salts synthesized above successfully trifluoromethylated enolate anions derived *in situ* from ketones with a base, with the exception of an enolate anion derived from 2-methyl-1-indanone, which has a tertiary α -carbon. The reactivity of the enolate anions may have been too great for these dibenzoheterocyclic salts. There-

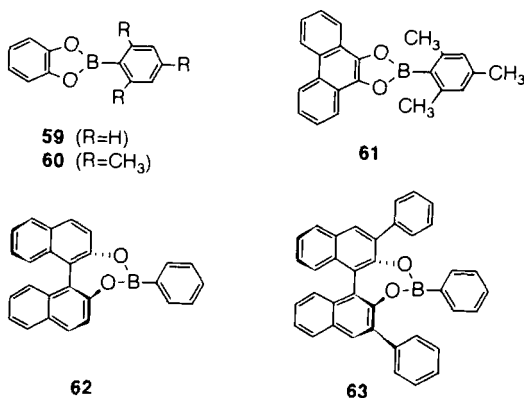
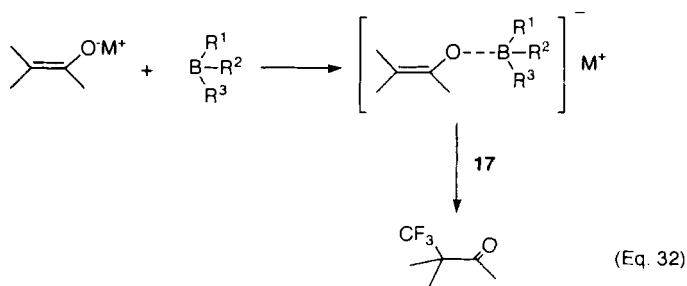
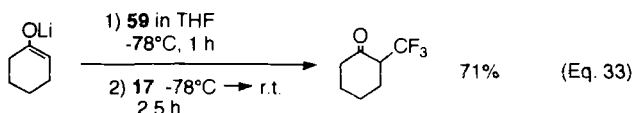


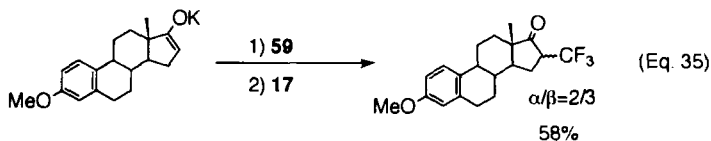
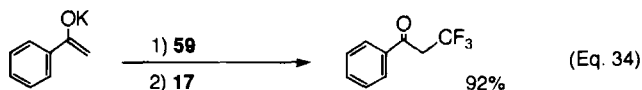
FIG. 2. Boron Lewis acids.

fore, the reactivity of the enolate anions was moderated by complexation with various boron Lewis acids to provide a more suitable match between the nucleophilicity of the enolate and the electrophilicity of the dibenzoheterocyclic salt. When the match was not suitable, decomposition of the heterocyclic salts occurred or the trifluoromethylation did not proceed. Thus, a new and versatile method for the trifluoromethylation of enolate anions by a suitable combination of *S*-salt **17** and boron Lewis acids **59–63** (Fig. 2) was presented (Eq. 32).

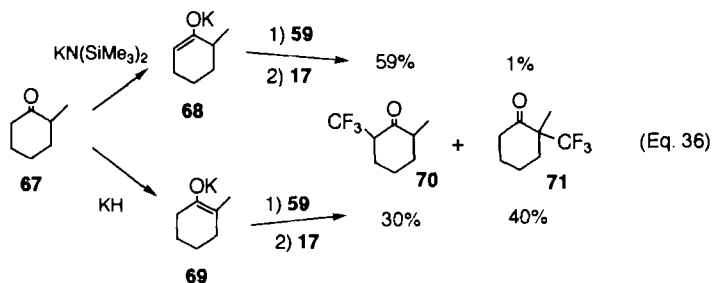


Various enolate anions were trifluoromethylated regioselectively in good yields by a combination of *S*-salt **17** with boron **59** (Eqs. 33–35).

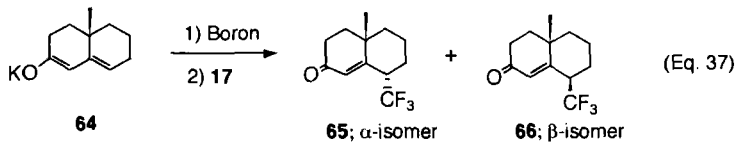




Enolate anion **68**, which was generated by kinetic deprotonation of ketone **67**, produced CF_3 ketone **70** almost exclusively, while enolate anion **69**, generated by thermodynamic deprotonation, gave a 3:4 mixture of **70** and **71** (Eq. 36).

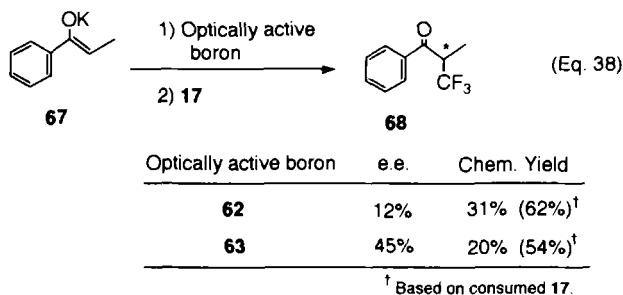


The stereoselectivity of the trifluoromethylation varied with the bulkiness of the boron reagent used. Thus, with enolate anion **64**, the product ratio of the thermodynamically less stable $\beta\text{-CF}_3$ isomer **66** versus the more stable $\alpha\text{-CF}_3$ isomer **65** increased with the bulkiness in the order $59 < 60 < 61$ (Eq. 37). This was explained by the conformation of the intermediate complexes.



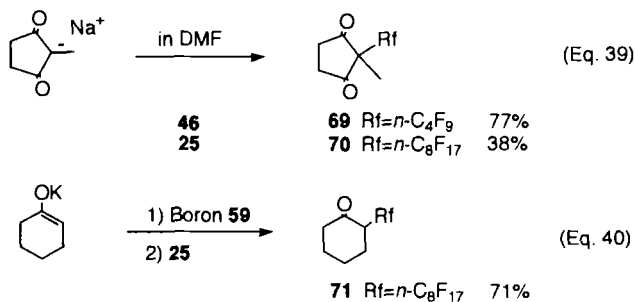
Boron	Yield	65 : 66
59	81%	1 : 2.5
60	50%	1 : 3
61	51%	1 : 4

Enantioselective trifluoromethylation was successful with new optically active borons **62** and **63**. Thus, enolate anion **67** of propiophenone was trifluoromethylated by a combination of **17** and **62**, and **17** and **63** to give CF₃-propiophenone **68** in 12 and 45% e.e., respectively (Eq. 38).



B. PERFLUOROBUTYLATION AND -OCTYLATION (93JA2156; 94JOC5692)

Perfluorobutylation and -octylation were carried out in the same manner as trifluoromethylation (Eqs. 39, 40).



VI. Kinetics of Trifluoromethylation (93UP2)

Kinetic studies of the trifluoromethylation of aniline with *S*-salt **17**, dinitro *S*-salt **39**, and nonheterocyclic *S*-salt **29** were carried out and the activation parameters determined (Table I).

The activation free energies ΔG^\ddagger obtained revealed the quantitative reactivity order of nonheterocyclic *S*-salt **29**, heterocyclic *S*-salt **17**, and dinitro heterocyclic *S*-salt **39** (**29** < **17** < **39**). The reaction with *S*-salt **17**

TABLE I
KINETIC PARAMETERS FOR THE TRIFLUOROMETHYLATION OF
ANILINE WITH *S*-(TRIFLUOROMETHYL)DIBENZOTHIOPHENIUM
TRIFLATE (**17**), *S*-(TRIFLUOROMETHYL)DIPHENYLSULFONIUM
TRIFLATE (**29**), AND *S*-(TRIFLUOROMETHYL)-3,7-
DINITRODIBENZOTHIOPHENIUM TRIFLATE (**39**) IN DMF-d₇
AT 25°C

Salt	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (eu)	ΔG^\ddagger (kcal/mol)
17	21.2	-11.2	24.5
29	12.1	-47.1	26.1
39	17.0	-9.1	19.7

was about 160 times faster than that of noncyclic *S*-salt **29** at 80°C. This is not explained by a lowered activation enthalpy ΔH^\ddagger , but by a greatly increased negative activation entropy ΔS^\ddagger of **17**. The high reactivity of **17** compared to **29** was initially attributed to the additional driving force due to the restoration of lost aromaticity by transformation of the central five-membered heterocyclic ring, regarded as having 4π -antiaromaticity, to a 6π -aromatic heterocycle (93JA2156), as discussed by Kevill and Anderson (91JOC1845) and Horak *et al.* (81JA289). However, the kinetic parameters indicate that the high reactivity of **17** is due to a steric factor (entropy term) in the transition state, not to the restoration of lost aromaticity. The highest reactivity of **39** is attributed to the decreased activation enthalpy ΔH^\ddagger caused by two strongly electron-withdrawing nitro groups in addition to the entropy term. The entropy term ΔS^\ddagger of **39** changes little from ΔS^\ddagger of **17**.

Kinetic studies of the *S*-methyl analogs *S*-methyldibenzothiophenium tetrafluoroborate (**72**) and *S*-methyldiphenylsulfonium tetrafluoroborate (**73**) were reported. The difference in ΔS^\ddagger between heterocyclic *S*-CH₃ salt **72** ($\Delta S^\ddagger = -13.4$ eu for ethanolysis) (91JOC1845) and nonheterocyclic *S*-CH₃ salt **73** ($\Delta S^\ddagger = -10.3$ eu at 25°C for *N*-methylation of pyridine-d₅) (83TL4859) was small. This is in accord with the conventional S_N2 attack mechanism of a nucleophile on the CH₃ carbon along the *S*-CH₃ bond. Thus, the great difference in ΔS^\ddagger found between heterocyclic *S*-CF₃ salt **17** and nonheterocyclic *S*-CF₃ salt **29** suggests a different reaction mechanism, probably an attack on the *S*-CF₃ bond.

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1,3-Oxazinium and 3-Azapirylium Salts

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I. Introduction	341
II. 5,6-Dihydro-4 <i>H</i> -1,3-oxazinium Salts	342
A. Synthesis	342
1. From Nonheterocyclic Compounds	342
2. From Other Heterocyclic Compounds	345
B. Reactions	346
III. 1,3-Oxazinium Salts	346
A. Synthesis	346
B. Benzoxazinium Salts	349
C. Reactions of 1,3-Oxazinium Salts	349
IV. 3-Azapirylium Salts	350
A. Synthesis	350
B. Reactions	352
1. Introduction	352
2. Hydrolysis	353
3. Recyclizations into Other Heterocycles	353
4. Reactions of Alkyl Substituents	355
C. Benzo-3-azapirylium Salts	357
V. 1,3-Oxazinium Salts Having Two Nitrogen Atoms	357
A. 1,3,5-Oxadiazinium Salts	358
B. 3,5-Diazapirylium Salts	358
1. Synthesis	358
2. Reactions	359
VI. Functionalized 1,3-Oxazinium Derivatives	360
A. Synthesis	360
B. Reactions	361
VII. Spectral Properties of 1,3-Oxazinium Derivatives	361
A. NMR Spectra	362
B. Infrared Spectra	362
References	363

I. Introduction

An active period of investigation of the positively charged 1,3-oxazine derivatives commenced in the early 1960s. At that time preparative methods

as well as conditions for the stabilization of highly active carbocations were discovered. Equally with other heterocyclic cations (e.g., pyrylium salts [82AHC(S)]), the 1,3-oxazinium systems came to be considered as interesting examples of stable heterocarbenium ions.

There are three principal series of 1,3-oxazinium derivatives with different unsaturation; namely, dihydro-1,3-oxazinium **1**, 1,3-oxazinium **2a,b**, and aromatic 3-azapyrylium salts **3** (see Scheme 1).

Some reviews characterize the former two types **1** and **2** as quaternized 1,3-oxazine compounds on the one hand, or as synthetic intermediates of the latter on the other [62HC(17)341; 72S333; 79MI1, 84MI1, 84S181]. Progress in the chemistry of 1,3-oxazinium derivatives was closely connected with Schmidt's work which was summarized in the most recent comprehensive review for all three compound types **1–3** (72S333).

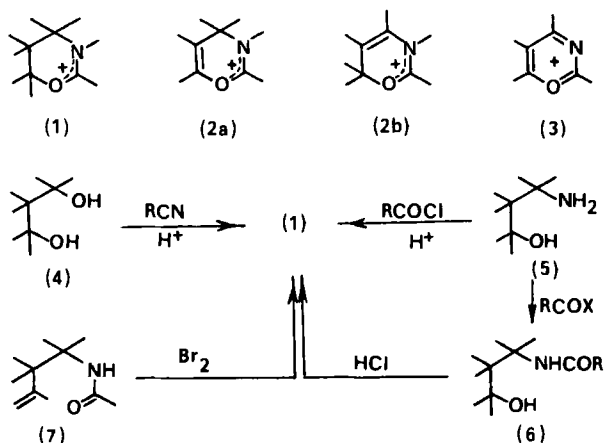
Many studies have been published in which new synthetic paths for 1,3-oxazinium and 3-azapyrylium salts as well as novel transformations of these compounds have been described. Such results permit one to consider the chemistry of 1,3-oxazinium cations to be a productive research field that deserves the attention of synthetic chemists.

II. 5,6-Dihydro-4*H*-1,3-oxazinium Salts

A. SYNTHESIS

1. From Nonheterocyclic Compounds

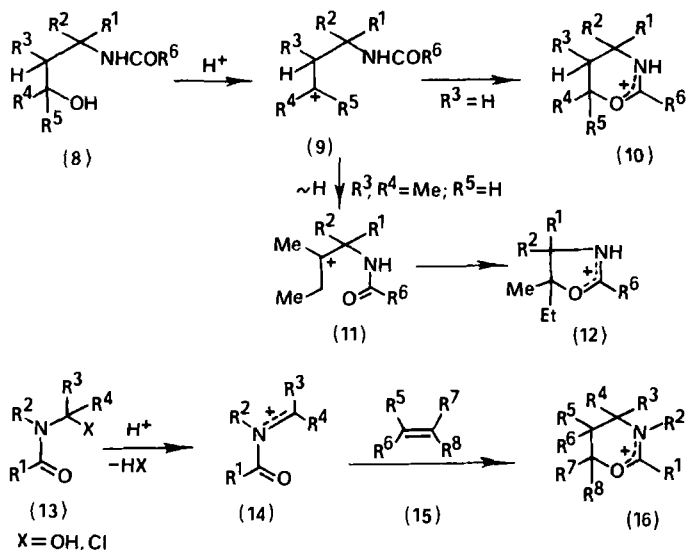
The earliest syntheses of 5,6-dihydro-4*H*-1,3-oxazinium salts **1** were two-component cyclization reactions three-carbon 1,3-bifunctional fragments



SCHEME 1

(e.g., 1,3-propanediol **4** or 3-aminopropanol **5**) and a C_1 -component. The latter may be a nitrile (Ritter reaction) or an acylating reagent (57JOC839; 59JOC711; 72S333). Some modifications of this approach consist in the application of *N*-acylated 3-aminopropanols **6** (61CB1657; 74JOC421) and of *N*-acylaminoalkenes **7** (76ZOR439) (Scheme 1).

It should be noted that the 1,3-bifunctional starting compounds **4–7** are quite difficult to obtain. Moreover, the direction of acid-catalyzed cyclization of 3-acylaminoalcohols depends considerably on their structure. Thus, *N*-acylaminoalcohols **8** can be cyclized to give either 5,6-dihydro-4*H*-1,3-oxazinanium salts **10** or 2-oxazoline derivatives **12** as well as mixtures thereof (82MI1, 82MI2; see also 78AHC1).

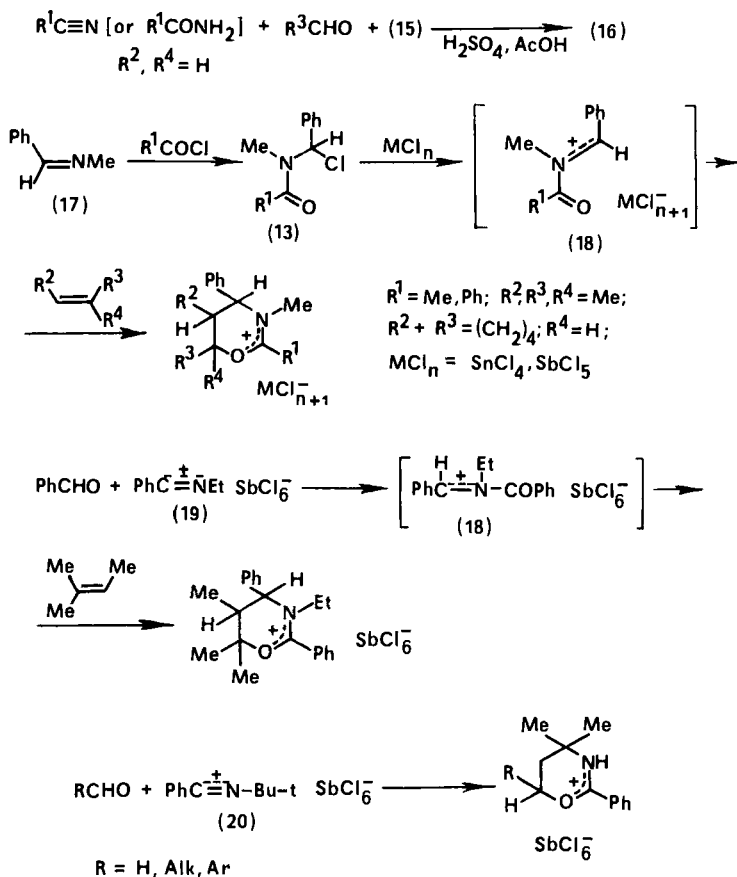


If the substituents R^4 or R^5 are phenyl groups, the intermediates **9** are quite stable benzyl cations, which can cyclize without isomerization. A hydrogen 1,2-shift is also disadvantageous energetically when $R^3 = H$. However, when $R^3 = R^4 = Me$ and $R^5 = H$, the rearrangement of the secondary ions **9** into more stable tertiary carbocations **11** takes place. This rearrangement changes the cyclization path, as in the transformation of 2-(*N*-acylaminoalkyl)cyclohexanols [**8**, $R^3 + R^4 = -(CH_2)_4-$, $R^5 = H$] exclusively into 2-oxazoline derivatives (82MI2). Interestingly, analogous acid-catalyzed cyclizations were observed in the reactions of acyloxycarbocations (Section IV,A) with olefins (86ZOR510).

The situation was changed by the discovery of a novel approach to the synthesis of 5,6-dihydro-4*H*-1,3-oxazinanium salts consisting in a polar 1,4-

cycloaddition of *N*-acyliminium ions **14** to olefins **15** (73AG235). This approach covers numerous syntheses of salts **16** that differ in the method of formation of intermediates **14**. The acidic ionization of *N*-hydroxymethyl- and *N*-chloromethylcarboxamides **13** was described in early work [66LA(697)171; 69AG576]. Alkenes, cycloalkenes, dienes, and cycloalkadienes as well as α , β -unsaturated carbonyl compounds were used as olefinic components **15** (70CB3242). An application of chiral *N*-acyliminium ions [**14**, $R^1 = \text{PhCH(OMe)-}$] provided evidence for a synchronous 1,4-cycloaddition mechanism (70AG322).

Subsequent development of this general approach was directed to the *in situ* formation of ions **14** from various precursors. As a result, a series of three-component one-pot syntheses of salts **16** has been created. The reactions of aldehydes with nitriles or amides to form amidoalkyl ions **14** are most applicable (Scheme 2) (70JAP70/24582; 71S92; 74G1181). The

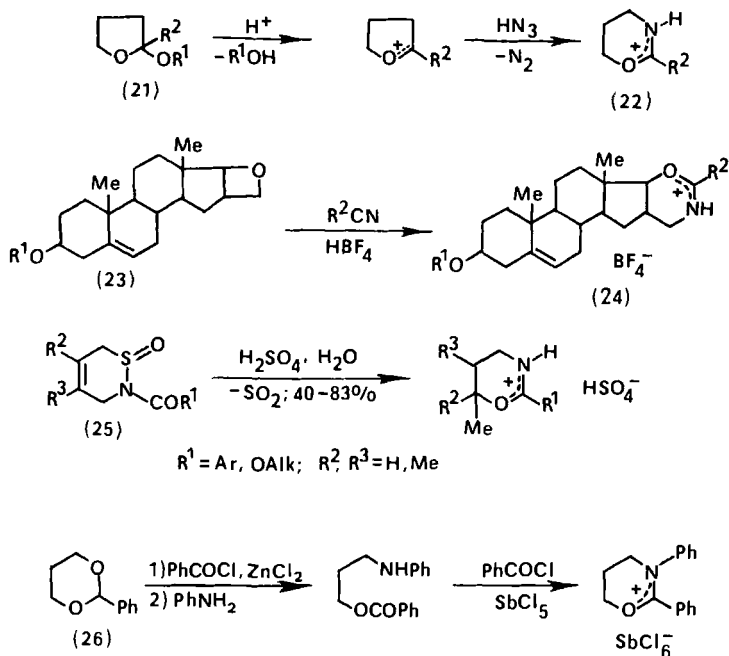


SCHEME 2

acylation of *N*-methyl benzaldimine **17** (70CB3242; 85TH1) and anodic oxidation of amides (75BSF389) were also proposed as methods of generating ions **14** and **18**. It was found recently that 5,6-dihydro-4*H*-1,3-oxazinium salts can be obtained by the interaction of diacetone alcohol with acetonitrile (89ZOR2416) as well as by reactions of aldehydes with nitrilium salts **19** and **20** (Scheme 2)(92ZOR2569). The use of the *N*-*tert*-butylnitrilium salt **20** is attractive because no olefinic component is required in this reaction due to the *in situ* formation of isobutylene from salt **20**. The use of *N*-acyliminium cations for cycloadditions has been described recently in reviews (89CRV1525; 94MI1).

2. From Other Heterocyclic Compounds

Only a few transformations of heterocycles into 5,6-dihydro-4*H*-1,3-oxazinium salts have been described. Tetrahydrofuran derivatives **21** were enlarged by inserting a nitrogen atom from HN_3 to form salts **22** (75T575). The steroid oxetanes **23** were converted into dihydro oxazines via the corresponding salts **24** (85T3377). The acid-catalyzed recyclization of 1-oxo-3,6-dihydro-1,2-thiazines **25** and the transformation of 2-phenyl-1,3-dioxane **26** are also interesting examples (76ZOR439; 78ZOR1092; 86KGS421).



B. REACTIONS

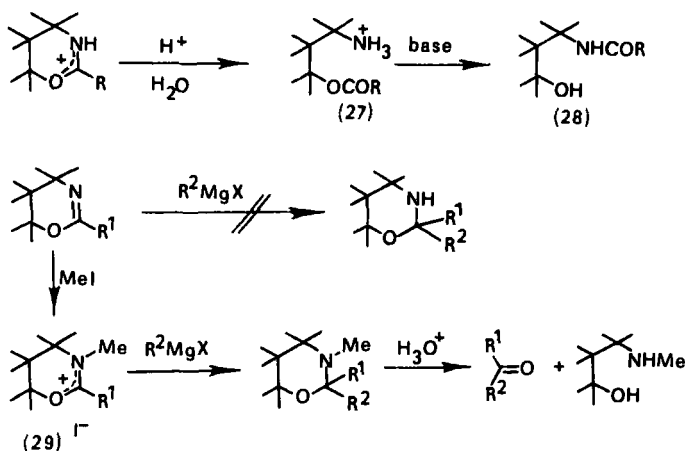
The 5,6-dihydro-4*H*-1,3-oxazinium salts are in essence cyclic alkoxy-carbenium ions bearing two heteroatoms at the carbenium center. They are similar to other heterocarbenium ions and have an ambident character which has been described in detail in reviews (64AG400; 72CRV357).

The development of convenient methods for the synthesis of the above-named salts opened the way to 1,3-aminoalcohol derivatives **27** and **28** [72S333; 85ACH(118)139]. The application of salts **29** as highly reactive C₁-components for the preparation of aldehydes and ketones is widely known (72JA3243, 72JOC4289, 72MI1; 73JOC175; 74MI1) (Scheme 3). The synthesis of valuable carbo- and heterocyclic and polyfunctional derivatives via dihydro oxazinium intermediates was also described (62AG866; 80CPB1178; 84CPB1433).

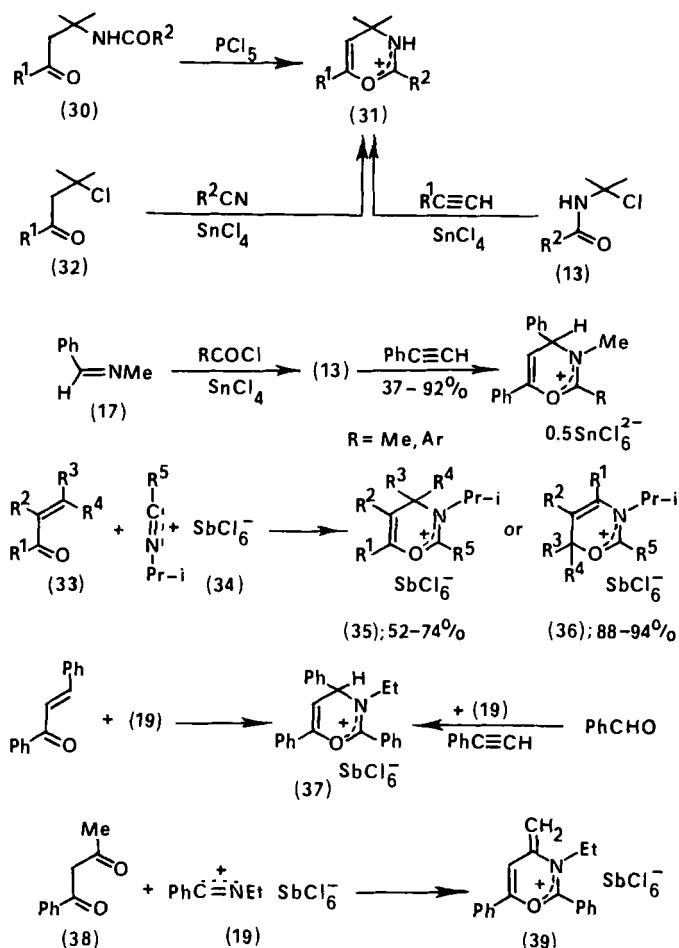
III. 1,3-Oxazinium Salts

A. SYNTHESIS

1,3-Oxazinium salts contain a carbon-carbon double bond in a ring and have a higher oxidation level than salts **1**. [For information about oxidation degrees and levels for organic compounds see Mathieu and Panico (72MI2).] Therefore, the two- and three-component syntheses of salts **2** and **31** are based on starting materials having a higher oxidation level than that of salts **1**. For instance, β -acylamino ketones **30** and acetylenes are being



SCHEME 3



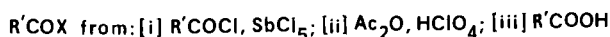
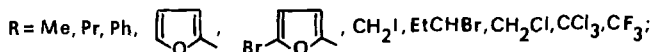
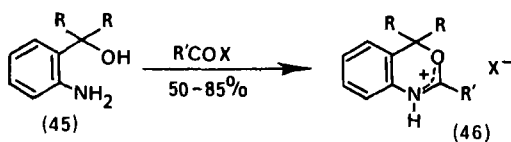
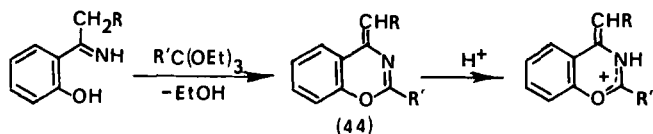
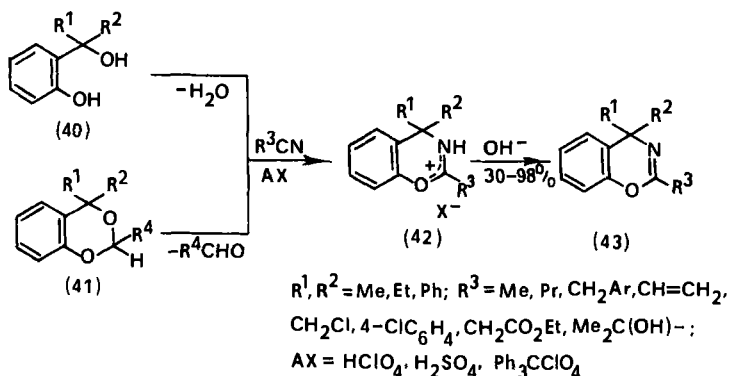
SCHEME 4

used instead of β -acylamino alcohols and olefins, respectively (64CB2234; 65AG218; 72S333) (Scheme 4).

Some work devoted to the synthesis of 1,3-oxazinium salts has been published. These salts are assumed to be intermediates in the acylation of olefins in the presence of nitriles (84ZOR1357; 87ZOR1546). This process corresponds to the interaction between β -chloroketones **32** and nitriles.

Schmidt predicted the possibility of forming 4H-1,3-oxazinium salts by reactions of α,β -unsaturated ketones with nitriles (72S333). It was realized recently and independently in Germany and in Russia that nitrilium salts **19** and **34** may be used (90S763; 91KGS568, 91MI1, 91T205). Either 4H-1,3-oxazinium salts **35** or 6H-isomers **36** may be obtained, depending on

the structure of starting ketones **33**. The relative stability of cationoid intermediates determines the different paths of interaction, which can include both the direct cyclization of adducts (**33** + **34**) and a rearrangement of the latter via a four-membered transition state (90S763). The reaction of benzaldehyde with nitrilium salt **19** (Section II,A,1) leads to 1,3-oxazinium salt **37** in the presence of phenylacetylene. Benzoylacetone (**38**) gives the stable 4-methylene-1,3-oxazinium salt **39** under the same conditions (91KGS568) (Scheme 4). The factors that determine the cyclization of cationoid intermediates into 1,3-oxazinium salts are not yet completely clear. Thus, *N*-acylaminopropyne $\text{PhCONH}-\text{CH}_2\text{C}\equiv\text{CH}$ forms 2-oxazoline derivatives instead of 1,3-oxazinium salts by the action of electrophiles (81TL3325).



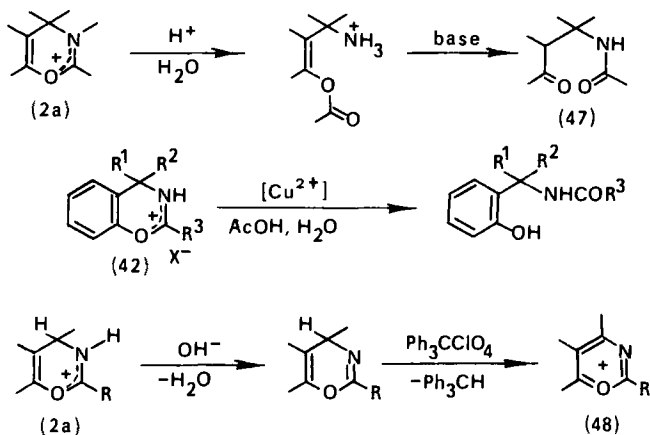
B. BENZOXAZINIUM SALTS

There are two types of benzo derivatives differently annulated; namely, benzo-4*H*-1,3-oxazinium **42** and benzo-4*H*-3,1-oxazinium salts **46**. Some information about uncharged benzoxazine systems has been summarized in a review [62HC(17)341]. The chemistry of the corresponding salts has been almost unknown.

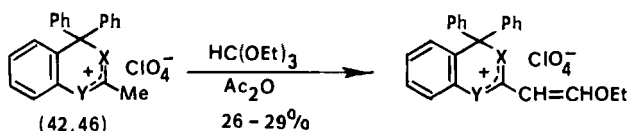
Systems **42** were assumed to be intermediates readily converted into benzoxazines **43** without isolation (68URP225197, 68ZOR119; 70KGS43, 70KGS1465; 72KGS303; 80KFZ35). More recently, the analogous reactions of 2-hydroxyphenylcarbinols **40** and of benzo-1,3-dioxanes **41** with nitriles were described; these occur by the known Ritter reaction scheme (78ZOR2184). Surprisingly, in another approach it is not the *exo*-methylene group, but rather the nitrogen atom that undergoes protonation in intermediate **44** (70CB2760). Acid-catalyzed acylation of 2-aminophenylcarbinols **45** leads to various benzo-4*H*-3,1-oxazinium salts **46** (84KGS953; 90KGS101; 93KGS537, 93KGS542, 93KGS547).

C. REACTIONS OF 1,3-OXAZINIUM SALTS

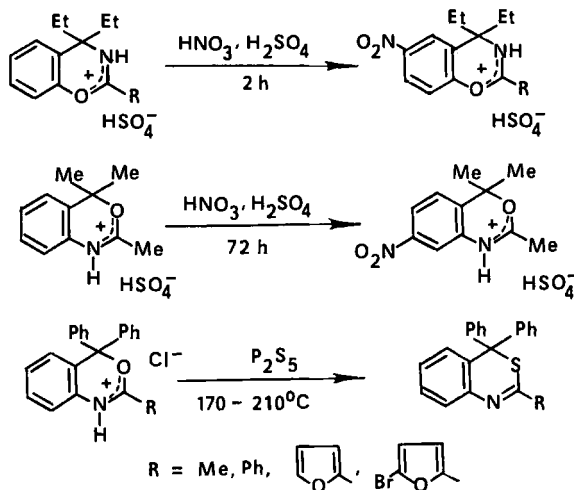
Valuable β -acylamino-carbonyl compounds **47** are obtained by the hydrolysis of monocyclic salts **2a** (72S333). The ring opening of benzo derivatives



42 is possible using copper salts (70KGS1465). Compounds **2a** bearing hydrogen atoms at positions 3 and 4 can be dehydrogenated in a two-stage process to form 3-azapyrylium salts **48** (65CB3892; 72S333; 79M11). Some



(42) $\text{X} = \text{NH}$, $\text{Y} = \text{O}$; (46) $\text{X} = \text{O}$, $\text{Y} = \text{NH}$



SCHEME 5

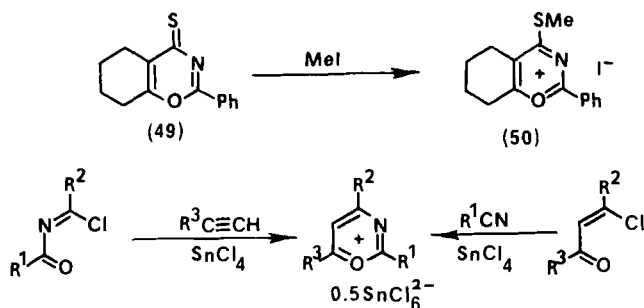
reactions of benzoxazinium salts are shown in Scheme 5 (72KGS303; 78ZOR2184; 93KGS537; 93KGS542).

IV. 3-Azapyrylium Salts

Among the 1,3-oxazinium derivatives, the 3-azapyrylium salts are the most interesting [they are also called $1^+-1,3$ -oxazinium (72S333), 1,3-oxazin-1-ium (83MI1), 1,3-oxazinium (78AHC1; 84MI1), and 1,3-oxazinylum salts (81BCJ2387)]. The absence of a universally accepted name for these compounds indicates the novelty of this field of heterocyclic cation chemistry.

A. SYNTHESIS

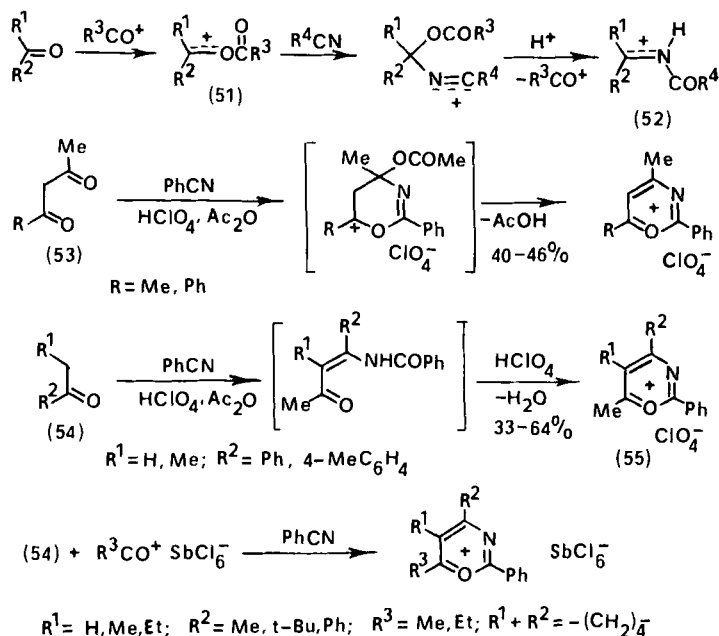
The first 3-azapyrylium salts **48** and **50** were obtained from other heterocycles by oxidative dehydrogenation (Section III,C) and by *S*-alkylation of 4-thiono-1,3-oxazine (**49**) (62CB937; 72S333). Until recently only two



SCHEME 6

methods based on polar 1,4-cycloaddition were known (Scheme 6) [69LA(723)111; 72S333; 73AG235]. However, these methods did not offer easy access to the 3-azapyrylium salts.

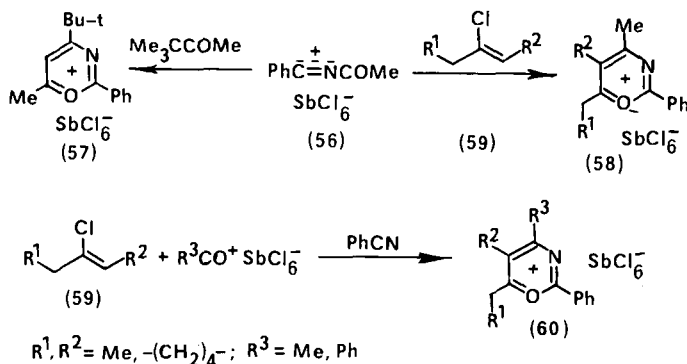
Progress was made by the discovery of electrophilic catalysis by acyl cations in carbonyl reactions (91ZOR1588). This catalysis type consists in the conversion of aldehydes or ketones into highly active acyloxycarbocations **51** by the addition of acyl cations regardless of the origin of the latter. In contrast to related hydroxy- and alkoxy carbocations ($\text{R}^1 \text{R}^2 \text{C}^+ - \text{OR}^3$,



SCHEME 7

$R^3 = \text{H, Alk}$), ions **51** are able to add the weakly nucleophilic nitriles to give *N*-acyliminium ions **14** and **52** (Section II,A,1)(89ZOR2416; 91MI1). This catalysis was used in the development of new methods for the synthesis of 3-azapyrylium salts from ketones **53** and **54** (Scheme 7).

It has been found that 3-azapyrylium salts **57** and **58** are obtained in reactions of pinacolone as well as vinyl chlorides **59** with *N*-acylnitrilium salt **56** (91ZOR2479; 92ZOR2577). The acylation of vinyl chlorides **59** in benzonitrile also leads to salts **60** (91ZOR1986). The same salts **55** are formed as intermediates by acylation of acetylenes in the presence of nitriles (88ZOR1605). Vinyl chlorides and acetylenes are both direct derivatives of carbonyl compounds with the same oxidation level (72MI2; 85KGS1443).



Various 3-azapyrylium salts differently substituted are now easy to prepare due to the novel synthetic methods described above.

B. REACTIONS

1. Introduction

Like the related pyrylium salts [82AHC1(S)1], aromatic 3-azapyrylium salts are very reactive toward nucleophiles. They have two reactive centers, positions 6 (preferably) and 2, in accordance with their charge distribution (87ZOR717). In the 1960s investigations were performed that drew a general picture of 3-azapyrylium transformations. These results were reflected in Schmidt's review (72S333). A few later reviews devoted to 1,3-oxazines just repeated the contents of the latter (78AHC1) or touched upon them casually (79MI1; 83MI1; 84MI1).

2. Hydrolysis

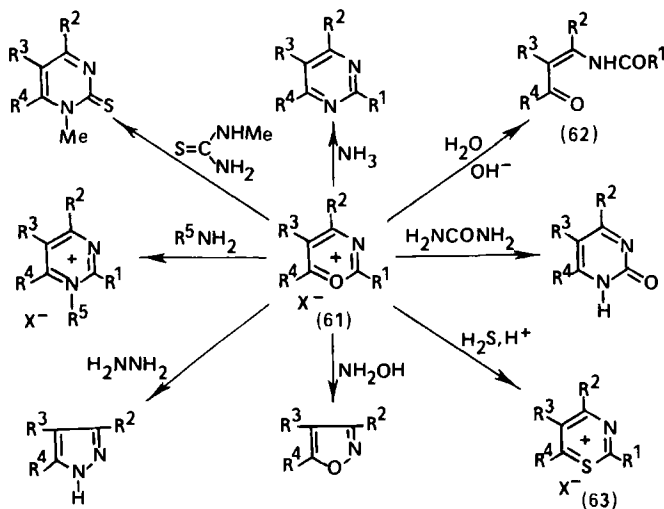
Salts **61** easily undergo ring opening by the action of bases to give β -acylaminovinyl ketones **62** (Scheme 8) [69LA(723)111; 88ZOR1561, 88ZOR1605; 91ZOR1986].

3. Recyclizations into Other Heterocycles

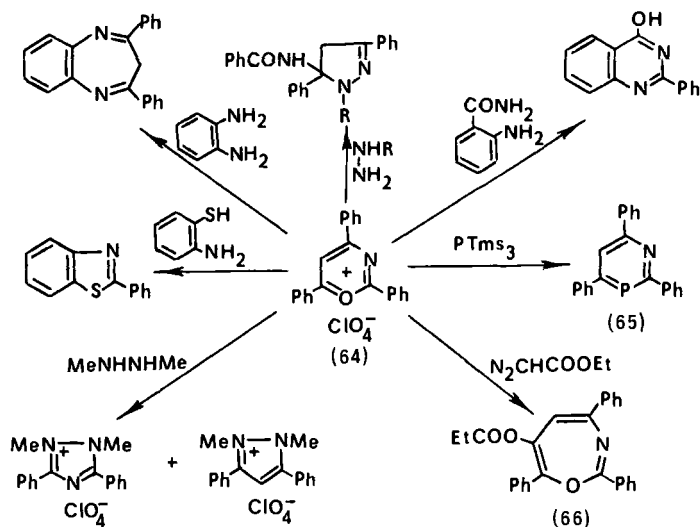
a. *Reactions with Heteronucleophiles.* Reactions of 3-azapyrylium salts with nitrogen-containing nucleophiles comprise their best known transformations. Some reaction paths for salts **61** are shown in Scheme 8 (72S333; 78AHC1; 91ZOR1986; 94TH1), including the conversion into 3-azathiopyrylium salts **63** which are also very reactive substances (69CB269; 79BCJ3767).

The reactions of 2,4,6-triphenyl-3-azapyrylium perchlorate (**64**) with various amino compounds were investigated in detail (Scheme 9) (81BCJ2387). Conversions into 3-phosphapyridines **65** and oxazepines **66** have been also described (74S187; 87TL1093) (Scheme 9).

b. *Reactions with Nucleophilic Carbon Compounds.* The conditions for reaction of 3-azapyrylium salts with phenols, enamines, Grignard reagents, and active methylene compounds leading to pyridines, 2-benzopyrylium salts, and other valuable derivatives were reported in reviews and some

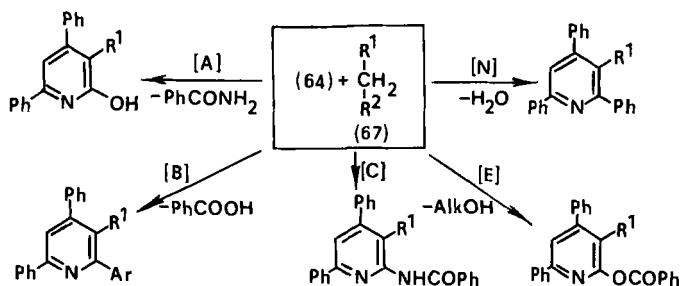


SCHEME 8



SCHEME 9

articles (65CB3892, 65TL4357; 69BCJ2382; 72S333; 78AHC1). Subsequently, the accurate investigation of the behavior of salts **64** in reactions with compounds **67** possessing active methylene groups was carried out (75BCJ73). The ring-openings and recyclization processes observed were divided to five characteristic modes that differ with the nature of the reagent **67** (Scheme 10). The interesting pyrimidopyrimidinium salts **70** and **72** were obtained from 6-methyl- and 2-methyl-substituted 3-azapyrylium salts **68** and **71** by the action of a mixture of DMF and Ac_2O (91KGS1556; 94TH1).



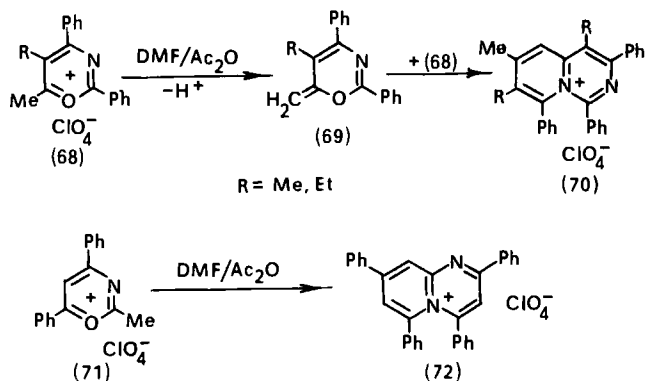
[A]: $\text{R}^1 = \text{CN}, \text{COOEt}, \text{COPh}$; $\text{R}^2 = \text{CONH}_2$;

[B]: $\text{R}^1 = \text{COAr}, \text{CN}, \text{CONH}_2$; $\text{R}^2 = \text{COAr}$;

[C]: $\text{R}^1, \text{R}^2 = \text{CN}$; [E]: $\text{R}^1 = \text{CN}, \text{COOEt}$; $\text{R}^2 = \text{COOAlk}$;

[N]: $\text{R}^1 = \text{NO}_2$, $\text{R}^2 = \text{H}$

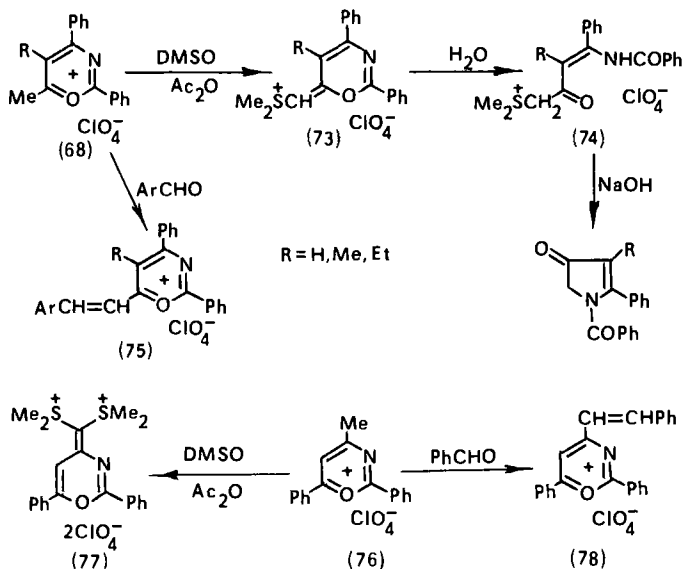
SCHEME 10



4. Reactions of Alkyl Substituents

Deprotonation of the α -position of a carbenium center is one of the most typical properties of carbocations. All the alkyl-substituted heterocyclic ions possess an appreciable CH-acidity [82AHC(S)1]; the 3-azapyrylium salts are no exceptions to this rule. The formation of anhydro bases, i.e., methylene-1,3-oxazines (e.g., **69**), from methyl-3-azapyrylium salts is well known (72S333).

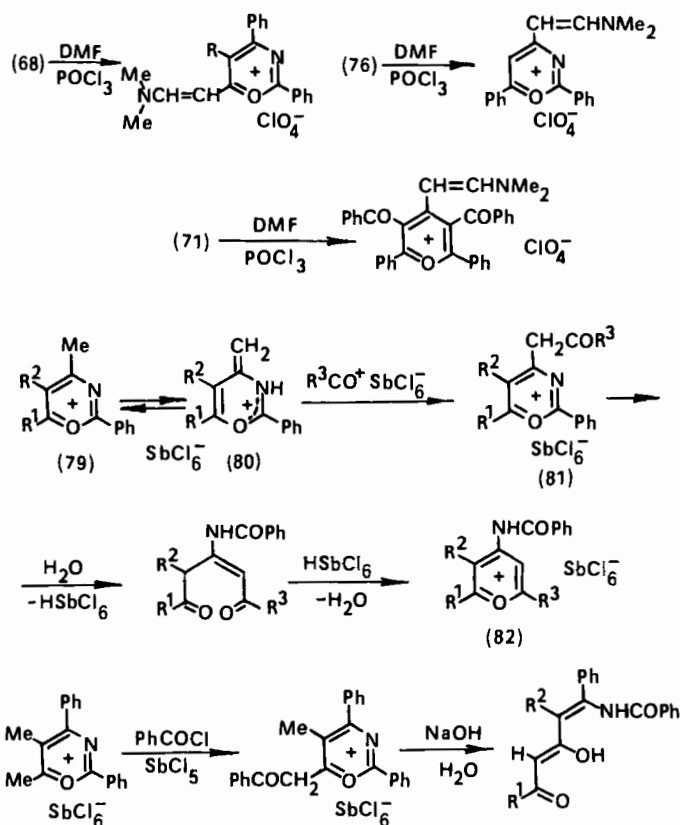
Later, a series of new transformations of alkyl-substituted 3-azapyrylium salts based on the CH-acidity of alkyl groups in positions 2, 4, and 6 of the



SCHEME 11

ring was described. Two examples of such reactions were shown above ($68 \rightarrow 70$ and $71 \rightarrow 72$). Like pyrylium salts [82AHC(S)1], compounds **68** and **76** react with aromatic aldehydes to give styryl derivatives **75** and **78** (94TH1) (Scheme 11). The heteroanalog of such carbonyl compounds—dimethyl sulfoxide—yields a series of cyclic and open-chain sulfonium salts **73**, **74**, and **77** (Scheme 11) (94TH1).

However, it is most surprising that alkyl-substituted 3-azapyrylium salts can undergo formylation and acylation at the side chain. These reactions are examples of the interaction of heterocyclic cations with cationoid electrophiles. Some of these processes are presented in Scheme 12 (90KGS134; 91KGS265; 94TH1). It is assumed that such transformations are possible due to the intramolecular deprotonation of the methyl group in **79** to form charged anhydro base **80** (see structure **39**). The 4-acylmethyl-3-

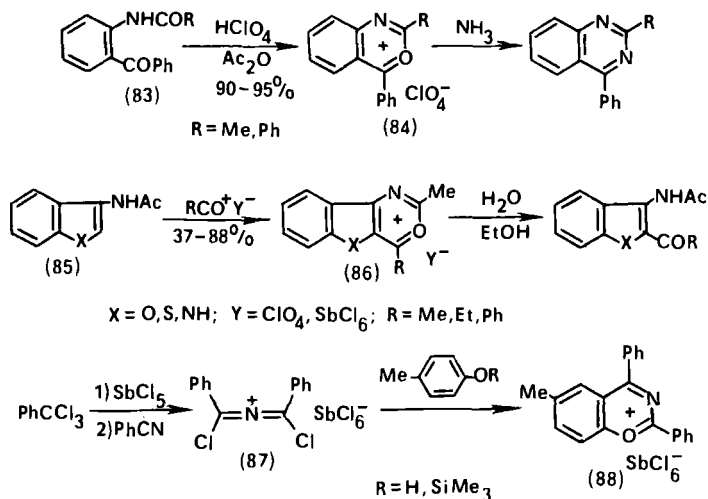


SCHEME 12

azapyrylium salts **81** can easily recyclize into 4-acylamino pyrylium salts **82**, which are usually difficult to prepare. It should be noted that these conversions that occur with the lengthening of a linear carbon chain can be considered to be the γ -functionalization of 1,3-dicarbonyl compounds because 3-azapyrylium salts are masked and activated forms of the latter (Scheme 12).

C. BENZO-3-AZAPYRYLIUM SALTS

This field has not been investigated extensively. Dehydration of 2-acylamino inobenzophenones **83** leads to benzo[*d*]-3-azapyrylium salts **84** previously



unknown (76 KGS1286; 76URP525678). Another approach to salts **86** consists in the acylation of acetylamino derivatives **85** of benzo[*b*]furan, benzo[*b*]thiophene, and indole (79URP697518; 90KGS1569). An unusual path for the formation of the benzoannulated 3-azapyrylium ring **88** was proposed using 2-azoniaallene cations **87** (89S918).

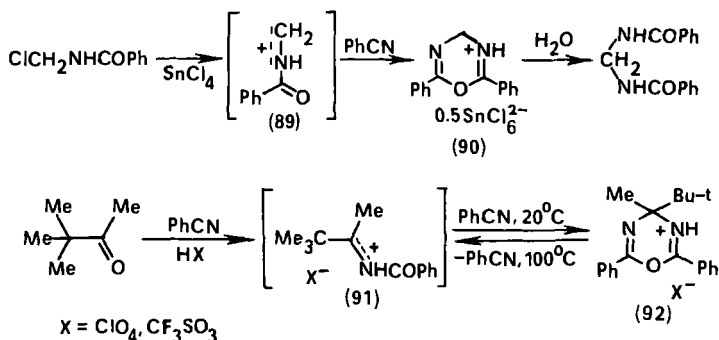
V. 1,3-Oxazinium Salts Having Two Nitrogen Atoms

The 1,3,5-oxadiazinium derivatives are heteroanalogs of the 1,3-oxazin-ium salts described above. They merit consideration because they can be

formed like the latter and can serve as precursors to many valuable compounds.

A. 1,3,5-Oxadiazinium Salts

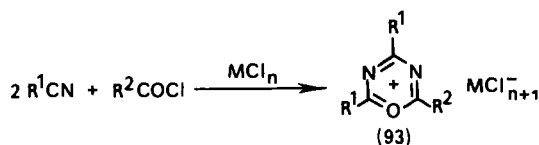
As mentioned above, the polar 1,4-cycloaddition of *N*-acyliminium ions **14** and **18** to olefins gives 5,6-dihydro-4*H*-1,3-oxazinium salts **16** (Section II,A,1), or forms the 1,3-oxazinium salts with acetylenes (Section III, A). The same ions **89** and **91** add nitriles to furnish 1,3,5-oxadiazinium salts **90** and **92**, little investigated until now (65CB334; 88ZOR230). Salts **92** are unstable and can dissociate at elevated temperatures with nitrile liberation. Therefore, they may serve as original reservoirs for active *N*-acyliminium cations.



B. 3,5-Diazapyrylium Salts

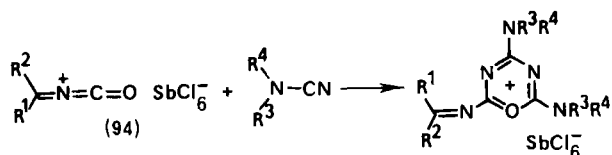
1. Synthesis

The aromatic 3,5-diazapyrylium salts **93** [also called 1,3,5-oxadiazinium (85CB1304, 85CB1887; 87TL353) and 1,3,5-oxadiazin-1-ium salts (83MI1)] are better known than salts **90** and **92**. They were first described by Meerwein (56CB209). Subsequently, the analogous reactions of various cyano compounds were carried out (65CB334; 66CB2454; 67CB3736; 78UK1814; 80ZOB2331; 81LA1198; 85CB1304; 86MI1, 86ZC94) (Scheme 13). In the last decade modifications of this general approach were first published using diacyl chlorides (87TL353; 88JHC1023) as well as 2-azaallenium ions **94** from α -chloro isocyanates (85CB1887; 88MI1) (Scheme 13).



$\text{R}^1 = \text{Ar}, \text{ArO}, \text{NAlk}_2, \text{AlkS}; \quad \text{R}^2 = \text{Me}, \text{Ar}, \text{CH}_2\text{Cl};$

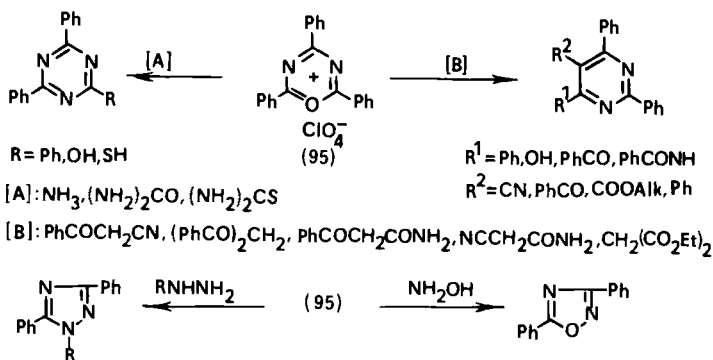
$\text{MCl}_n = \text{SbCl}_5, \text{SnCl}_4, \text{AlCl}_3$



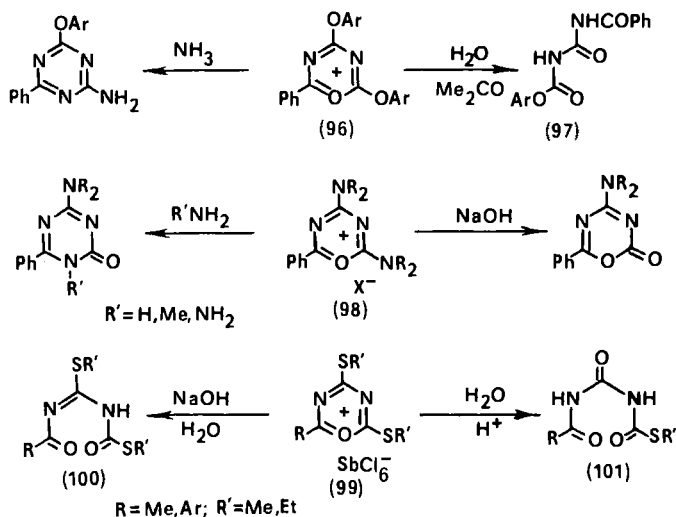
SCHEME 13

2. Reactions

Various transformations of salts **95** are shown in Scheme 14 (65CB334; 69BCJ2382; 73BCJ3902; 83MI1). Some reactions of functionally substituted 3,5-diazapyrylium salts **96**, **98**, and **99** can be seen in Scheme 15 (67CB3736; 81LA1198; 86ZC95, 86ZC132). In these ways the allophan acid derivatives **97**, **100**, and **101** are obtained.



SCHEME 14

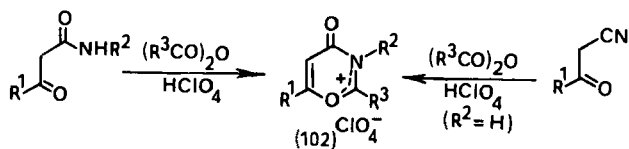
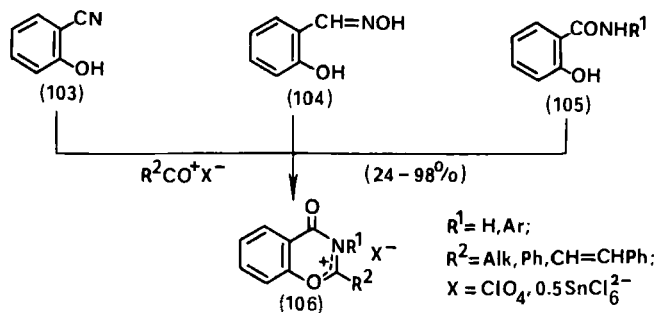


SCHEME 15

VI. Functionalized 1,3-Oxazinium Derivatives

A. SYNTHESIS

3,5-Diazapyrylium salts bearing various hetero groups (NR₂, OR, SR) are shown in Section V,B. Some amino-substituted 3-azapyrylium salts were


$$R^1 = \text{Me, Et}; R^2 = \text{H, Ar}; R^3 = \text{Me, Ph} \quad [50-95\%]$$


also described (87M1383). However, almost all the publications in this field are devoted to oxo derivatives (e.g., 87M1263; 91T205). Among these are three articles that considered the synthesis of monocyclic 1,3-oxazin-4-onium salts **102** (also named 4-oxo-1,3-oxazinium) previously unknown (77KGS704, 77ZOR2459; 81H851).

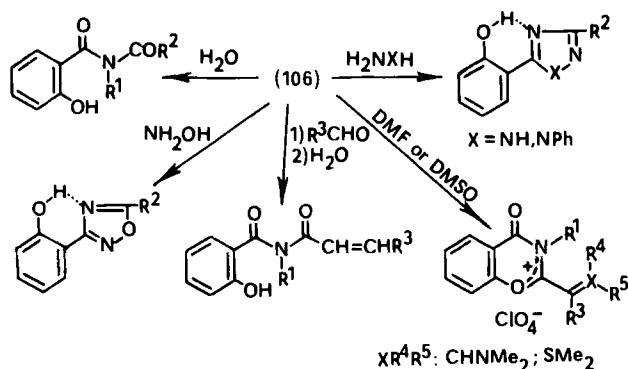
Benzoannulated 1,3-oxazine-4-onium salts **106** were first mentioned by Shemyakin *et al.* (65T3537) and become available after investigations of acylation of salicylonitrile (**103**), salicylaldoxime (**104**), and salicylamides **105** [74ZOB2792, 74ZOR2233; 75KGS280, 75KGS460, 75KGS1184, 75ZOB1860; 76KGS742; 79KGS1611; see also 70TL5095; 81ACS(B)465].

B. REACTIONS

Some transformations leading to valuable compounds (e.g., light-sensitive and biologically active derivatives) are shown in Scheme 16 (75KGS1184, 75ZOB1860; 77KGS47, 77KGS322, 77KGS328, 77KGS704, 77ZOR2459; 78KGS161; 81KGS1423; 83KGS406; 91BSB175, 91BSB487; 92ZOR579).

VII. Spectral Properties of 1,3-Oxazinium Derivatives

Information concerning the spectral characteristics of 1,3-oxazinium derivatives discussed above is scant. Systematic investigations have not been carried out. In work devoted to the synthesis of 5,6-dihydro-1,3-oxazinium, 1,3-oxazinium, and benzo-1,3-oxazinium salts, these products underwent deprotonation without identification or even isolation. Such articles contain only the spectra of the corresponding uncharged 1,3-oxazines. A few recent publications describe these salts as individual compounds.



SCHEME 16

A. NMR SPECTRA

Some ^1H -NMR characteristics unsuitable for generalizations are listed in articles considering 5,6-dihydro-4*H*-1,3-oxazinium salts (89ZOR2416; 92ZOR2569), 1,3-oxazinium salts (90S763; 91KGS568), benzo-1,3-oxazinium salts (78ZOR2184), and 4-oxo-1,3-oxazinium salts (77KGS704, 77ZOR2459).

The ^1H -NMR spectra of 3-azapyrylium salts are very similar to those for pyrylium salts [82AHC(S)1]. The chemical shifts of methyl groups in positions 4, 5, 6 of a 3-azapyrylium ring ($\delta = 2.98\text{--}3.3$, $2.23\text{--}2.61$, and $2.6\text{--}3.18$ ppm, respectively) almost coincide with the corresponding values for α -, β -, and δ -methyl groups in pyrylium salts (64JCS1646; 88ZOR1561, 88ZOR2232; 90KGS134; 91ZOR1986, 91ZOR2479). Such similarities were noted for 2- and 4-ethyl groups as well as for 4-*tert*-butyl groups in both types of salts [82AHC(S)1; 91ZOR1986, 91ZOR2479].

The restricted rotation about exocyclic partial double bonds in some 3-azapyrylium salts was investigated by temperature-dependent ^{13}C - and ^1H -NMR spectroscopy (87MRC688).

The ^{13}C -NMR spectra of some dialkylamino-substituted 3,5-diazapyrylium salts were discussed (85CB1887; 88JHC1023).

The oxo structures of 1,3-oxazin-4-onium and benzo-1,3-oxazin-4-onium salts, but not their 4-hydroxy forms, have been confirmed by ^1H -NMR spectra in which the chemical shifts of methyl groups in position 2 were almost identical for both NH- and NMe-substituted salts **106** (75KGS460; 77KGS328, 77KGS704, 77ZOR2459).

B. INFRARED SPECTRA

Intense bands appear between 1620 and 1630 cm^{-1} in vibrational spectra of 5,6-dihydro-4*H*-1,3-oxazinium salts **1**. The fragment $\text{O}-\overset{+}{\text{C}}-\text{N}$ may be responsible for this vibration. *N*-Protonated salts **1** have IR spectra with a wide band at $3305\text{--}3380\text{ cm}^{-1}$ (NH^+) (89ZOR2416; 92ZOR2569).

A moderately intense band at $1665\text{--}1700\text{ cm}^{-1}$ appears in the IR spectra of 4*H*-1,3-oxazinium salts **2a** which can be ascribed to $\text{C}=\text{C}$ double bond of the ring (90S763; 91KGS568).

The bands at 1640 and 1725 cm^{-1} in the IR spectra of 1,3,5-oxadiazinium salt (**92**) correspond to vibrations of $\text{O}-\overset{+}{\text{C}}-\text{N}$ and $\text{C}=\text{N}$ fragments, respectively (89ZOR2416). Unfortunately, the IR spectral characteristics are often not identified (i.e., the bands are simply listed) or are contradictory (84KGS953; 93KGS537, 93KGS542).

The spectra of aromatic 3-azapyrylium salts **3** are very much like those for pyrylium salts [82AHC(S)1; 88ZOR2232; 91ZOR1986]. Benzoannellated

3-azapyrylium systems give vibrational spectra resembling those of 2-benzopyrylium salts (90AHC157, 90KGS1569). The aromatic cation is responsible for bands at 1608–1640 cm^{-1} .

Quite a detailed discussion of the IR spectra for 3,5-diazapyrylium salts **93** was published (80ZOB2331). These spectra do not contain ring bands above 1650 cm^{-1} . Three or four intense bands at 1640–1540 cm^{-1} attributed to aromatic ring vibrations were found. The strong bands at 1460, 1390, 1340, and 1180 cm^{-1} were believed to be due to vibrations of C—O and C—N bonds (80ZOB2331; 88JHC1023).

The 4-oxo-1,3-oxazinium salts and their benzo derivatives are characterized by a very strong band at 1730–1770 cm^{-1} attributed to C=O bond vibrations. Such an abnormally high frequency was explained by an increase in the C=O bond order due to an electron-density shift from the carbonyl oxygen to the ring (80TH1).

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